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## Original Communications

### STUDIES ON CONGESTIVE HEART FAILURE

#### I. THE IMPORTANCE OF RESTRICTION OF SALT AS COMPARED TO WATER


HENRY A. SCHROEDER, M.D.
NEW YORK, N. Y.


THERE is fairly general agreement as to the importance of restricting fluids in the treatment of congestive heart failure, but in the matter of the restriction of sodium chloride, and to what extent it should be restricted, there is difference of opinion. Some textbooks[1] advocate rigid restriction of fluids. Osborne and Fishbein, and others,[2] advise restriction of both fluids and salt, although little investigation has been done to substantiate this advice. Various "cardiac diets" in general use are relatively poor in salt, and the limitation of fluids is widely practiced in the treatment of heart failure when edema is present. Although in normal man there may be an excess of tissue fluid after the ingestion of a large amount of salt, but not of water,[3] it is uncertain whether salt, fluids, or both, are necessary factors in the occurrence or prevention of the edema of heart failure. An attempt has been made, therefore, to learn the importance of each of these substances.

Twenty-three patients were selected for study, and an attempt was made to find the most obstinate cases of congestive heart failure. Patients were given weighed diets, in which the content of sodium chloride (calculated from Sherman's tables[4]) the caloric value, the protein content, and the intake of fluid were constant for definite periods.* The amount of activity to which the patient had been accustomed prior to study was not changed, so that spontaneous diuresis as a result of rest might be avoided. Digitalis was given when auricular fibrillation with a rapid ventricular rate was present, or when the patient had previously


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*The value of the diets used was usually 2,000 calories (in order to prevent change in weight from loss of body substance), although occasionally 1,500 calories were given. The protein content was as high as was consistent with the amount of salt, i.e., 70-80 Gm. in a diet containing 1.0 Gm. of NaCl, or 35-40 Gm. in one containing 0.5 Gm. The amount of water in the food was calculated, and was found to vary but little; it was not included in the total intake of fluids shown in the charts. Unless previously under prolonged observation, the patients were usually observed in the hospital for two weeks on a standard regime, without changes being made, before they were studied.

been taking it. Diuretic drugs were administered only when the condition of the patient necessitated their use. The output of chloride in the urine was measured daily (Volhard-Arnold method).

*The Action of Sodium Chloride.*—It was observed in all cases that a reduction in the amount of ingested salt was followed by a loss in weight and in edema fluid (Table I). Often diuresis and loss of weight began immediately when the intake of sodium chloride was reduced from 2.0 Gm. in twenty-four hours to 1.0 Gm.* In obstinate cases in which the edema was of long standing, it was always possible to prevent the accumulation of fluid by restriction of salt, although occasionally this necessitated a diet containing as little as 0.5 Gm. in twenty-four hours.

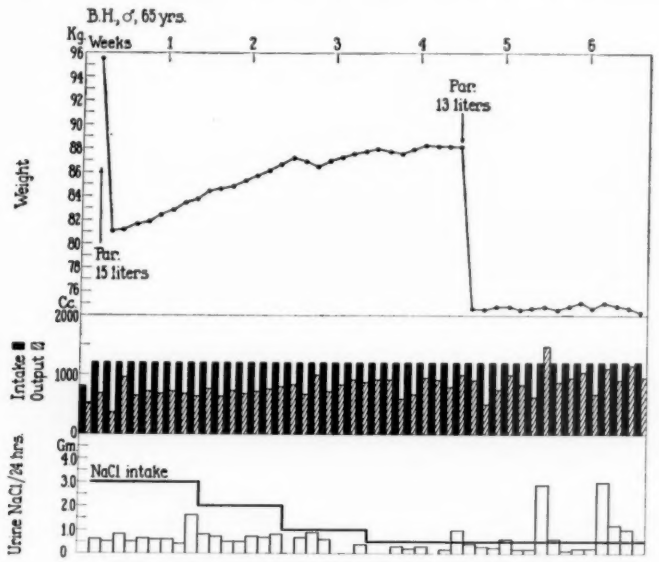


Fig. 1.—Case 8. B. H., aged 65, suffered from heart failure for three years after an attack of coronary occlusion. There was an enormous ascites; paracentesis had to be done twenty-nine times. Digitalis, mercurial diuretics, ammonium chloride, and various other measures had been of no avail. Auricular fibrillation, with a slow ventricular rate, was present. There was edema in dependent tissues. At "Par," 15 liters were removed from the abdomen. Following this, on an intake of 3.0 Gm. of NaCl, he gained 471 Gm. a day; on 2.0 Gm., 386 Gm. a day; on 1.0 Gm., 114 Gm. a day; on 0.5 Gm., 29 Gm. a day. Thirteen liters were then removed from the abdomen, and his weight remained constant for six weeks. He became free of edema after various diuretics had been given; his body weight was 60 kg. Edema could then be controlled by a diet containing 1.0 Gm. of NaCl. Edema recurred slowly after discharge from the hospital. The diet contained 0.5 Gm. NaCl, to which extra salt was added during the first three weeks. He was ambulatory during the period of observation.

The addition of a small amount of salt to the diet (1.0 Gm. to 2.0 Gm.) was followed, on the other hand, by an immediate gain in weight. By changing the quantity of salt in the diet, without varying the food, the intake of fluids, or the patient's activity, the weight and the amount of

*The amount of sodium chloride in the diet was calculated exactly, according to the tables of Sherman. It is probable that foods obtained from different sources and localities may vary in their content of sodium chloride, and that these figures may not be accurate. Foods were, therefore, obtained from the same sources insofar as possible, and these amounts of sodium chloride are probably constant. When patients refused part of their diet it was subsequently given to them in other forms, in order that the total intake per day should remain constant.

edema could be controlled at will. That a reduction in the intake of salt will result in lessening of the accumulation of edema in obstinate cases of congestive heart failure can be demonstrated (Fig. 1).

*The Action of Fluids.*—It was found that the intake of fluids had little relation to the accumulation or disappearance of edema when the intake of salt was low enough. Weight was gained more rapidly in an occasional case when salt was not severely restricted and the intake of fluids forced (Fig. 2*B*), but, on the administration of a minimal amount of sodium chloride, weight was lost and edema disappeared as rapidly on a regime of restriction of fluids as on one in which water was freely given (Table II). There was, in fact, no effect on varying the intake of fluids even in cases of severe chronic congestive heart failure (Fig. 2, *A* and *B*). In only two cases was a sudden increase in the intake of fluids followed by a gain in weight and failure of the output of urine to increase.

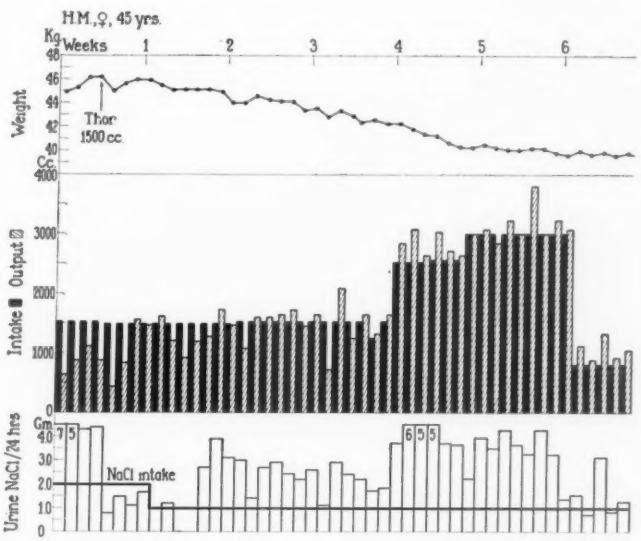


Fig. 2.—*A*, Case 16. H. M., a woman aged 45, had suffered from chronic congestive heart failure for six years; her first attack of cardiac failure occurred after she was 34. She had acute rheumatic fever at 18. For four years she had been bedridden because of continuous edema, ascites, and hydrothorax. Mercurial diuretics, squills, and digitalis had not controlled her heart failure, and she had rarely been free of edema. There were signs of involvement of the mitral, tricuspid, and aortic valves, and auricular fibrillation, requiring the use of digitalis, was present. She was given a diet containing 1.0 Gm. of NaCl, to which extra salt was added as needed.* On an intake of 2.0 Gm., in spite of the removal of 1.5 liters of fluid from her chest there was a slight gain in weight. On 1.0 Gm. there was an immediate loss, which continued. When the fluid intake was increased from 1500 c.c. a day to 2500, slight diuresis occurred. It was then increased to 3000. She was free of edema, but there remained a moderate amount of fluid in the chest. Reduction of the intake of fluid to 800 c.c. a day resulted in no further loss of weight.

*The rather high excretion of chlorides during the first four days probably represents ammonium chloride which the patient had been taking.

Both patients exhibited marked diminution of renal function. But in every other case without organic renal disease, under these conditions the amount of water ingested did not affect the course of the illness (Fig. 3), with the exception of a few instances in which its limitation appeared

sometimes to result in an adverse change in the weight curve (Cases 16, 17, 18, 19).

*The Choice of a Diet.*—In most instances 1.0 Gm. of sodium chloride in the diet was found to be low enough to prevent edema, but in a few cases, in which the heart failure was of long duration and the edema continuous, it was necessary to reduce the intake of salt to 0.5 Gm. per day. By measuring the excretion of chlorides in the urine it was possible to estimate the degree of restriction of sodium chloride which would be necessary for an effect, and a diet containing less than the amount excreted was used. Patients for whom 1.0 Gm. of salt per day was too much were sometimes able to tolerate that amount when compensation had been restored on a smaller intake (of salt).

A diet containing 0.5 Gm. of sodium chloride per day is inadequate in its protein content and cannot be given for a long period of time. A diet in which the salt content is 1.0 Gm. is adequate except for vitamins, and these should be added. Samples of the diets employed are shown (Table III).

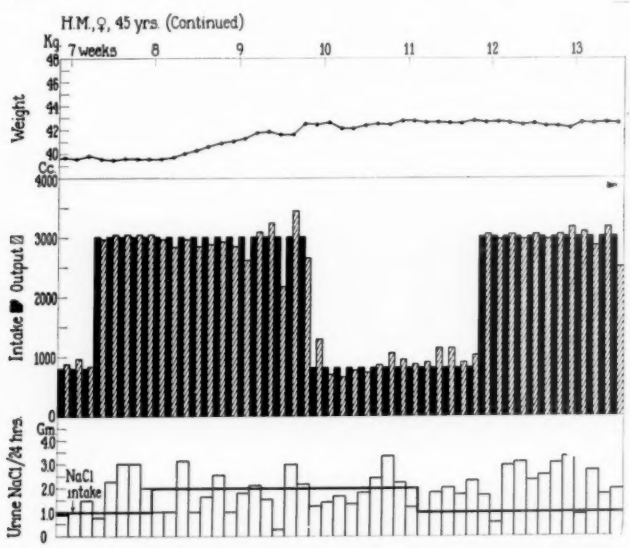


Fig. 2.—*B*, Same patient, continued. The intake of fluids was suddenly increased from 800 c.c. to 3000 c.c. a day without change in body weight. However, when 1.0 Gm. of NaCl was added to the diet a slow gain in weight resulted; this was accompanied by dyspnea, discomfort, and recurrence of edema. Reduction in the intake of fluids to 800 c.c. a day was immediately followed by a slight loss of weight for one day, but the gain continued, although more slowly. When the extra salt was removed from the diet the weight again became constant, and, when the intake of fluids was increased to 3000 c.c. a day, a slight loss resulted. This patient remained free of edema for five months under observation in the hospital, and for four months at home. She was unable to keep to her diet for three weeks, took considerable extra salt, and immediately suffered a recurrence of congestive heart failure and died. At autopsy, marked rheumatic involvement of the mitral, tricuspid, and aortic valves was found. The patient was in bed during the period of observation.

*Disturbances Associated With a High Intake of Fluids.*—In two cases, already mentioned, in which there was a diminution of renal function, with retention of nitrogen in the blood and severe disease of the liver, the rapid increase in the intake of fluids was accompanied by no increase

in the output of urine for several days. These patients complained of weakness, prostration, muscular cramps, and drowsiness, and gained weight rapidly. The chlorides of the plasma in one case were found to be markedly diminished; in the other no measurements were made. When the intake of fluids was subsequently reduced, diuresis occurred and weight was lost. It was believed that these symptoms represented "water intoxication," that is, dilution of electrolytes caused by failure to excrete ingested water. When renal function was normal a rapid increase in the intake of fluids was accompanied by an increase in the output of urine. Patients who were suffering from attacks of paroxysmal dyspnea or pulmonary edema did not have an increase in the number of attacks when the intake of fluids was high.

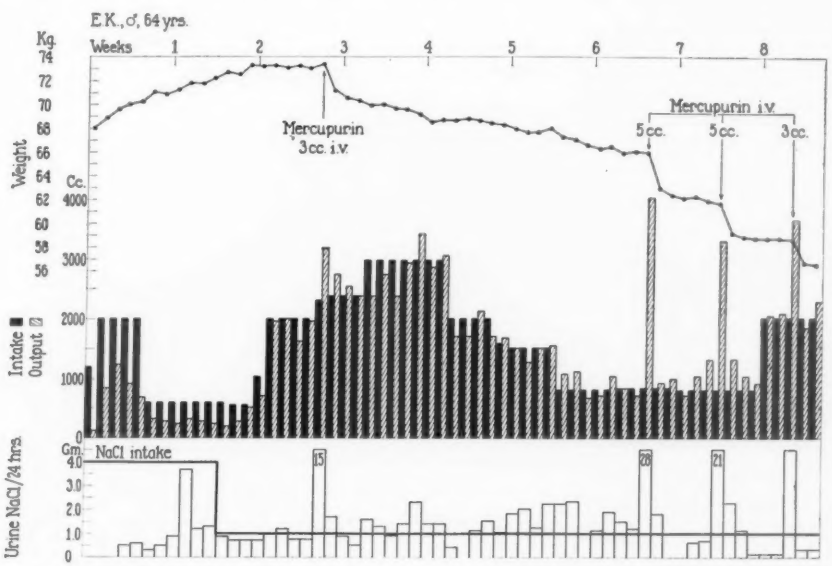


Fig. 3.—Case 18. E. K., a man, aged 64, had suffered from chronic congestive heart failure for fifteen years, and had been continually edematous for six years while under observation; he required 4 to 6 c.c. of mercupurin or salyrgan every two to three weeks. There were marked edema in dependent tissues and moderate ascites. He was given a diet containing 1.0 Gm. of NaCl, to which extra salt was added. On 4.0 Gm. of NaCl and 2000 c.c. of fluid a day, his gain in weight was rapid, and it continued, although less rapidly, when the intake of fluids was 600 c.c. a day. Even after reducing the amount of NaCl to 1.0 Gm., there was a slight gain, but an increase in the intake of fluids to 2000 c.c. a day resulted in no further change. Because of discomfort, 3.0 c.c. of mercupurin (half his usual dose) were given intravenously, and this initiated diuresis. This did not appear to be influenced by the amount of fluids ingested, but continued at the same rate whether 3000 c.c. or 800 c.c. a day were given. The sudden increase again from 800 c.c. to 2000 c.c. a day resulted in no change in weight. The patient subsequently died of cerebral hemorrhage. He was ambulatory during the period of observation.

## DISCUSSION

Water may act as a diuretic, and salt and water as an antidiuretic. Peters[5] describes the mechanism in these words: "Presumably, when water alone is given, the concentration of water in the serum is increased, and that of salt diminished to such an extent that the kidneys are stimulated to excrete more than the usual amount of water. . . . The adminis-

TABLE I

EFFECT OF INTAKE OF SODIUM CHLORIDE ON THE WEIGHT OF PATIENTS WITH CONGESTIVE HEART FAILURE

| CASE NO. | NAME & SEX | AGE YR. | DURATION HEART FAILURE MONTHS | SIGNS OF HEART FAILURE* | | | NaCl. INTAKE† GM./DAY | FLUID INTAKE C.C./DAY | NO. DAYS OBSERVATION | WEIGHT CHANGE KG. | AVERAGE WEIGHT CHANGE GM./DAY | REMARKS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | EDEMA | ASCITES | HYDRO-THORAX | | | | | | |
| 1 | E. H. ♂ | 73 | 2 | ++ | 0 | 0 | (5) | 1500 | 21 | −0.4 | −19 | Arteriosclerotic heart disease. |
| | | | | ++ | 0 | 0 | (2) | 1500 | 7 | −1.0 | −143 | Complete heart block. |
| | | | | 0 | 0 | 0 | (2) | ad lib. | 23 | −4.0 | −174 | |
| | | | | 0 | 0 | 0 | ad lib. | ad lib. | 9 | +3.0 | +333 | |
| | | | | 0 | 0 | 0 | (2) | ad lib. | 11 | −1.5 | −136 | |
| 2 | E. H. ♀ | 89 | 2 | + | 0 | 0 | ad lib. | ad lib. | 20 | +5.0 | +250 | Arteriosclerotic heart disease. |
| | | | | + | 0 | 0 | (2) | 1500 | 46 | −3.0 | −65 | Mild congestive heart failure. |
| 3 | M. C. ♀ | 64 | 12 | ++ | 0 | 0 | (3) | 2000 | 9 | −3.2 | −356 | Arteriosclerotic heart disease. |
| | | | | ± | 0 | 0 | (2) | 2000 | 7 | −2.6 | −371 | Pulmonary emphysema. Aortic |
| | | | | 0 | 0 | 0 | (2) | 1500 | 15 | −3.2 | −213 | stenosis. |
| 4 | R. G. ♂ | 56 | 2 | ++ | 0 | 0 | (4) | 1400 | 20 | +3.6 | +180 | Hypertension. Slight renal in- |
| | | | | + | 0 | 0 | (2) | 1400 | 12 | −7.2 | −600 | sufficiency. |
| 5 | M. W. ♂ | 62 | 3 | ++ | 0 | 0 | (4) | 1200 | 4 | +1.0 | +250 | Arteriosclerotic heart disease. |
| | | | | ++ | 0 | 0 | (2) | 1200 | 11 | −1.8 | −164 | |
| 6 | J. B. ♂ | 68 | 18 | ++ | 0 | 0 | (3) | 1200 | 11 | −1.1 | −100 | Arteriosclerotic heart disease. |
| | | | | 0 | 0 | 0 | 1 | 1200 | 11 | −2.9 | −264 | |

*Signs of heart failure, i.e., at end of period.

†NaCl intake per day. Where indicated by ( ), the actual content of sodium chloride in the diet was not calculated daily, but was estimated from sample diets, and is, therefore, approximate. When not so indicated, the content was calculated daily and was constant during the period of observation.

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 7 | P. O. ♂ | 65 | 12 | +++ | 0 | 0 | (2) | 1200 | 10 | +1.2 | +120 | Complete heart block. Syphilis. Arteriosclerosis. |
| | | | | ++ | | 0 | 1 | 1200 | 11 | −3.8 | −345 | |
| | | | | 0 | | 0 | (2) | 800 | 8 | −0.5 | −63 | |
| | | | | ++ | | + | 0.5 | 800 | 9 | −2.3 | −256 | |
| | | | 2 | ++ | 0 | + | 1 | 1800 | 12 | −4.0 | −333 | |
| | | | | 0 | 0 | 0 | ad lib. | 1800 | 10 | +1.0 | +100 | |
| | | | | 0 | 0 | 0 | 1 | 1800 | 10 | −1.5 | −150 | |
| 8 | B. H. ♂ | 65 | 36 | ++ | ++ | 0 | 3 | 1200 | 7 | +3.3 | +471 | Arteriosclerotic heart disease. Auricular fibrillation, slow ventricular rate. |
| | | | | ++ | +++ | 0 | 2 | 1200 | 7 | +2.7 | +386 | |
| | | | | +++ | ++++ | 0 | 1 | 1200 | 7 | +0.8 | +114 | |
| | | | | +++ | ++++ | 0 | 0.5 | 1200 | 7 | +0.2 | +29 | |
| | | | | +++ | ++ | 0 | 0.5 | 1200 | 14 | 0 | 0 | |
| 9 | H. P. ♂ | 47 | 1 | +++ | 0 | + | 3.0 | 1500 | 8 | +0.6 | +75 | Arteriosclerotic heart disease. Old coronary occlusion. |
| | | | | ++ | 0 | + | 1.0 | 1500 | 7 | −1.3 | −186 | |
| 10 | L. S. ♀ | 41 | 2 | ++ | 0 | + | 3.0 | 1500 | 7 | 0 | 0 | Rheumatic heart disease. Mitral stenosis. Tricuspid insufficiency. Auricular fibrillation. |
| | | | | + | 0 | 0 | 1.0 | 1500 | 10 | −5.0 | −500 | |
| 11 | M. K. ♀ | 49 | | 0 | 0 | 0 | (2) | 2000 | 10 | −0.3 | −30 | Rheumatic heart disease. Mitral stenosis. Auricular fibrillation. Incipient heart failure. |
| | | | | + | 0 | 0 | (4) | 2000 | 7 | +2.6 | +371 | |
| | | | | 0 | 0 | 0 | (2) | 2000 | 10 | −2.1 | −210 | |

TABLE II

EFFECT OF INTAKE OF FLUIDS AND OF SODIUM CHLORIDE ON WEIGHT OF PATIENTS WITH CONGESTIVE HEART FAILURE

| CASE NO. | NAME & SEX | AGE YR. | DURATION HEART FAILURE YR. | SIGNS OF HEART FAILURE* | | | NaCl. INTAKE† GM./DAY | FLUID INTAKE C.C./DAY | NO. DAYS OBSERVATION | WEIGHT CHANGE KG. | AVERAGE WEIGHT CHANGE GM./DAY | REMARKS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | EDEMA | ASCITES | HYDROTHORAX | | | | | | |
| 12 | A. J. ♂ | 52 | 9 | +++ | ++ | 0 | 1 | 1200 | 16 | +2.7 | +170 | Rheumatic heart disease |
| | | | | +++ | 0 | | 0.5 | 2500 | 4 | 0 | 0 | Mitral and tricuspid stenosis |
| | | | | ++ | 0 | | 0.5 | 2500 | 5 | −0.2 | −40 | |
| 13 | I. Y. ♂ | 57 | 5 | 0 | + | +++ | 1 | 1500 | 7 | −1.3 | −186 | Arteriosclerotic heart disease |
| | | | | 0 | 0 | + | 1 | 2400 | 7 | −0.5 | −71 | Old coronary occlusion |
| | | | | | 0 | 0 | 1 | 1200 | 8 | −0.2 | −25 | |
| 14 | J. H. ♂ | 58 | 6 | +++ | 0 | 0 | 2 | 2000 | 4 | −0.3 | −75 | Rheumatic heart disease |
| | | | | ++ | 0 | 0 | 1 | 2000 | 6 | +0.3 | +50 | Auricular fibrillation (20 yr.) |
| | | | | ± | 0 | 0 | 1 | 2000 | 6 | 0 | 0 | |
| | | | | ± | 0 | 0 | 1 | 1500 | 11 | −3.4 | −309 | |
| | | | | 0 | 0 | 0 | 1 | 2600 | 9 | −1.6 | −179 | |
| 15 | G. A. ♂ | 48 | 1 | ++++ | 0 | ++ | (2) | 2000 | 11 | −2.5 | −227 | Hypertension, with renal insufficiency |
| | | | | +++ | 0 | + | (2) | 3000 | 12 | −2.1 | −175 | |
| | | | | ++ | 0 | + | (2) | 2000 | 13 | −1.5 | −115 | |
| 16 | H. M. ♀ | 45 | 11 | +++ | +++ | +++ | 2 | 1500 | 8 | +3.1 | +388 | Rheumatic heart disease |
| | | | | + | + | ++ | 1 | 1500 | 18 | −3.7 | −206 | Mitral tricuspid stenosis |
| | | | | 0 | ± | + | 1 | 2500 | 7 | −2.0 | −286 | Auricular fibrillation |
| | | | | 0 | 0 | + | 1 | 3000 | 8 | −0.6 | −75 | |
| | | | | 0 | 0 | + | 1 | 800 | 8 | −0.3 | −38 | |
| | | | | 0 | 0 | + | 1 | 3000 | 6 | 0 | 0 | |
| | | | | + | + | ++ | 2 | 3000 | 14 | +2.0 | +143 | |
| | | | | 0 | 0 | + | 2 | 800 | 7 | +0.1 | +14 | |
| | | | | 0 | 0 | + | 1 | 800 | 7 | −0.1 | −14 | |
| | | | | 0 | 0 | + | 1 | 3000 | 7 | −0.5 | −71 | |
| 17 | R. L. ♀ | 69 | 5 mo. | +++ | + | + | 1 | 1500 | 20 | −2.4 | −120 | Arteriosclerotic heart disease |
| | | | | ++ | 0 | 0 | 1 | 800 | 15 | −2.3 | −153 | |
| | | | | + | 0 | 0 | 1 | 2000 | 18 | −3.0 | −167 | |

*Signs of heart failure, i.e., at end of period.

†NaCl intake per day. Where indicated by ( ), the actual content of sodium chloride in the diet was not calculated daily, but was estimated from sample diets, and is, therefore, approximate. When not so indicated, the content was calculated daily and was constant during the period of observation.

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 18 | E. K. ♂ | 64 | 18 | +++ | +++ | 0 | 4 | 2000 | 4 | +1.3 | +325 | Arteriosclerotic heart disease |
| | | | | +++ | +++ | 0 | 4 | 600 | 6 | +2.6 | +433 | |
| | | | | +++ | +++ | 0 | 1 | 600 | 4 | +0.5 | +125 | |
| | | | | | | | 1 | 2000 | 4 | −0.2 | −50 | |
| | | | | +++ | +++ | 0 | 1 | 2400 | 3 | −1.3 | −433 | |
| | | | | +++ | +++ | 0 | 1 | 3000 | 7 | −1.3 | −186 | |
| | | | | ++ | ++ | 0 | 1 | 2000 | 5 | −0.3 | −60 | |
| | | | | ++ | ++ | 0 | 1 | 800 | 8 | −1.1 | −137 | |
| 19 | M. J. ♀ | 44 | 12 | ++ | ++ | 0 | 1 | 1200 | 9 | −1.2 | −133 | Hypertension |
| | | | | ++ | ++ | 0 | 1 | 2400 | 9 | −0.1 | −11 | Long-standing heart failure |
| | | | | ++ | ++ | 0 | 1 | 3000 | 3 | +0.2 | +67 | Arteriosclerosis |
| | | | | ++ | ++ | 0 | 0.5 | 3000 | 5 | −0.3 | −60 | Auricular fibrillation |
| | | | | ++ | ++ | 0 | 1 | 2000 | 5 | −1.6 | −320 | |
| | | | | ++ | + | 0 | 1 | 1200 | 5 | +0.3 | +60 | |
| 20 | W. H. ♂ | 58 | 1 | +++ | +++ | ++ | 1 | 1200 | 13 | −1.2 | −923 | Arteriosclerotic heart disease |
| | | | | +++ | +++ | ++ | 1 | 1800 | 7 | +0.8 | +114 | Old coronary occlusion |
| | | | | +++ | +++ | ++ | 1 | 600 | 9 | −0.6 | −67 | |
| | | | | ++ | + | + | 1 | 600 | 9 | +0.3 | +33 | |
| | | | | ++ | + | + | 1 | 1200 | 5 | +0.8 | +160 | |
| 21 | E. H. ♀ | 69 | 6 mo. | ++ | 0 | +++ | 1 | 1500 | 11 | −1.3 | −118 | Arteriosclerotic heart disease |
| | | | | | | | 1 | 2000 | 7 | +0.5 | +71 | |
| 22 | C. M. ♂ | 11 | 18 mo. | ++++ | +++ | 0 | 1 | 1200 | 5 | −0.1 | −20 | Acute rheumatic fever |
| | | | | | | | 1 | 700 | 11 | −1.3 | −118 | Mitral and tricuspid insufficiency and stenosis |
| 23 | F. R. ♀ | 48 | 2 | +++ | 0 | 0 | 1 | 800 | 6 | −3.1 | −602 | Hypertension. Obesity |
| | | | | ++ | 0 | 0 | 1 | 2000 | 8 | −2.2 | −275 | Pituitary dyscrasia (?) |
| | | | | + | 0 | 0 | 1 | 1500 | 8 | −1.0 | −125 | |
| 4 | R. G. ♂ | 56 | 3 mo. | + | 0 | 0 | (2) | 1400 | 21 | +3.1 | +148 | Hypertension, with slight renal |
| | | | | 0 | 0 | 0 | (2) | 2000 | 29 | +3.1 | +107 | insufficiency |
| 7 | P. O. ♂ | 66 | 3 mo. | ++ | 0 | ± | 1 | 1000 | 12 | +0.8 | +67 | Arteriosclerosis. Syphilis |
| | | | | ++ | 0 | ± | 1 | 3000 | 5 | +3.2 | +604 | Complete heart block |
| | | | | ++ | 0 | ± | 1 | 1000 | 6 | 0 | 0 | Urea clearance 20 per cent |
| 8 | B. H. ♂ | 65 | 3 | ++ | ++ | 0 | 0.5 | 1200 | 7 | +0.1 | +14 | Arteriosclerotic heart disease |
| | | | | | | | 0.5 | 2500 | 4 | +3.5 | +875 | Old coronary occlusion |
| | | | | | | | 0.5 | 1200 | 5 | −2.5 | −500 | Urea clearance 25 per cent |

TABLE III

SAMPLE DIET CONTAINING 2,000 CALORIES AND 0.5 GM. NaCl

| | FOOD (grams) | PROTEIN (grams) | NaCl (mg.) | CALORIES |
|---|---|---|---|---|
| *Breakfast* | | | | |
| Bread | 45 | 4.2 | 34 | 116 |
| Butter | 12 | 0.1 | 2 | 87 |
| Jelly | 20 | 0.1 | 7 | 48 |
| Cream | 40 | 0.9 | 31 | 153 |
| Sugar | 12 | -- | -- | 48 |
| Canned apricots | 50 | 0.5 | 49 | 37 |
| Cream of wheat | 120 | 1.3 | 2 | 44 |
| *Dinner* | | | | |
| Steak (sirloin) | 45 | 9.9 | 107 | 52 |
| Rice | 25 | 2.0 | 16 | 88 |
| Butter | 10 | 0.1 | 2 | 73 |
| Fresh string beans | 75 | 1.8 | 35 | 32 |
| Butter | 5 | 0.1 | 1 | 37 |
| Apple, raw (sauce) | 100 | 0.4 | 28 | 63 |
| Sugar | 10 | -- | -- | 40 |
| Whipped cream | 20 | 0.4 | 15 | 76 |
| Lemon juice | 20 | -- | 3 | 8 |
| Lactose (drink) | 40 | -- | -- | 160 |
| *Supper* | | | | |
| Bread | 45 | 4.2 | 34 | 116 |
| Butter | 12 | 0.1 | 2 | 87 |
| Jelly | 20 | 0.1 | 7 | 48 |
| Steamed Irish potato | 90 | 1.8 | 50 | 77 |
| Butter | 10 | 0.1 | 2 | 73 |
| Lettuce | 20 | 0.2 | 10 | 3 |
| Pot cheese | 25 | 5.2 | -- | 28 |
| Fresh tomato | 50 | 0.5 | 16 | 12 |
| Olive oil | 15 | -- | -- | 135 |
| Canned cherries | 75 | 0.8 | 44 | 67 |
| Candy | 55 | 0.1 | 4 | 194 |
| | 1,066 | 34.9 | 501 | 2,002 |

tration of normal saline provokes the kidneys to no extra activity, because it does not appreciably alter the composition of the serum." Adolph[6] analyzes the actions of salt and water as follows: "If water is drunk, an equal amount is excreted usually within two or three hours in the urine, in addition to the water excreted at the normal rate. Meanwhile, the insensible loss of water increases in rate so that the body often ends up by having as little or less water than it would have had if none had been ingested. The same result is obtained from drinking a solution of almost any salt in a concentration that is osmolar with the blood. But if the salt is sodium chloride or sodium bicarbonate, then little or no diuresis results and the excess fluid is eliminated very slowly (during twenty-four to forty-eight hours)." According to Peters and Van Slyke,[7] "Retention of base entails retention of water, and accumulation of water is associated with storage of base. When the water changes affect chiefly the extracellular fluids, the base simultaneously retained or lost is chiefly sodium."

Therefore, there is good reason for rigid restriction of sodium chloride in chronic congestive heart failure. Edema fluid is composed principally of water and salt.[7] Considerable water is necessary in the economy of

TABLE III—CONT'D

SAMPLE DIET CONTAINING 2,000 CALORIES AND 1.0 GM. NaCl

| | FOOD (grams) | PROTEIN (grams) | NaCl (mg.) | CALORIES |
|---|---|---|---|---|
| *Breakfast* | | | | |
| Bread | 40 | 3.7 | 30 | 104 |
| Butter | 12 | 0.1 | 2 | 87 |
| Jelly | 15 | -- | 5 | 35 |
| Cream | 40 | 0.9 | 31 | 153 |
| Sugar | 15 | -- | -- | 60 |
| Canned apricots | 50 | 0.5 | 49 | 37 |
| Cream of wheat | 120 | 1.3 | 2 | 44 |
| Egg (boiled) | 50 | 6.6 | 179 | 80 |
| *Dinner* | | | | |
| Bread | 40 | 3.7 | 30 | 104 |
| Butter | 12 | 0.1 | 2 | 87 |
| Jelly | 15 | -- | 5 | 35 |
| Steak (sirloin) | 90 | 19.9 | 213 | 105 |
| Rice | 20 | 1.6 | 13 | 71 |
| Butter | 15 | 0.2 | 3 | 111 |
| Fresh string beans | 75 | 1.8 | 35 | 32 |
| Butter | 4 | -- | -- | 29 |
| Apple, raw (sauce) | 95 | 0.4 | 27 | 60 |
| Sugar | 10 | -- | -- | 40 |
| Whipped cream | 25 | 0.6 | 19 | 96 |
| *Supper* | | | | |
| Bread | 40 | 3.7 | 30 | 104 |
| Butter | 12 | 0.1 | 2 | 87 |
| Jelly | 15 | -- | 5 | 35 |
| Roast turkey | 60 | 19.0 | 203 | 97 |
| Steamed Irish potato | 75 | 1.5 | 42 | 64 |
| Butter | 12 | 0.1 | 2 | 87 |
| Lettuce | 20 | 0.2 | 10 | 3 |
| Fresh tomato | 50 | 0.5 | 16 | 12 |
| Pot cheese | 25 | 5.2 | -- | 28 |
| Olive oil | 5 | -- | -- | 45 |
| Canned cherries | 75 | 0.8 | 44 | 67 |
| | 1,132 | 72.5 | 999 | 1,999 |

the organism, but excess salt is not. Water cannot be deposited in the tissue spaces without salt. Salt is, therefore, necessary for the formation of this type of edema.

The rationale for the rigid restriction of fluids is not clear. If the intake of water is limited and the patient dehydrated, the deposition of edema should be lessened. Although dehydration can result from this procedure, it is uncertain that diuresis is thereby initiated. In these cases the output of urine was markedly depressed when the intake of fluids was low, and diuresis was not established until an adequate amount of fluid was administered. Furthermore, if edema can be prevented by the restriction of water, that substance must be rigidly restricted, but this cannot be continued for long without serious consequences. The free water contained in a diet of 2,000 calories may amount to a liter or more, and the "water of metabolism" to an additional 200 c.c. Limitation of this water necessitates a limitation of food which may, for short periods, be practicable, but obviously not for prolonged treatment. A certain volume of urine is necessary, furthermore, for the optimum excretion of chlorides (approximately 60 c.c. per hour). If the volume is permitted

to shrink below this the output of chlorides is lessened.[8] The opposite course is, therefore, preferable. If the output of urine can be increased by the administration of water, accompanied by rigid restriction of salt, the depletion of chlorides would be accelerated. On this plan, in no case did the output of urine fail to increase when extra water was added. Sometimes an increase in the amount of water taken actually initiated increased excretion of chlorides, which was accompanied by loss of weight. Conversely, the oliguria which accompanied severe restriction of fluids was associated with a decreased excretion of chlorides in the urine.

It is evident from these data that the administration of comparatively large amounts of fluid to cardiac patients does not increase the rate of formation of edema, provided the intake of salt is low enough. Under these conditions, Newburgh[9] and Schemm[10] have given cardiac patients considerable volumes of water without observing deleterious results. It is likely, therefore, that restriction of only one of the components of edema fluid is necessary for the control of anasarca. Limitation of the ingestion of salt, including limitation of those foods in which the salt content is high, imposes little hardship upon the patient, whereas restriction of fluids to the degree necessary to produce an effect may be difficult, hazardous, and uncomfortable. The occasional diuresis, with loss of weight, which has been observed when fluids were given suggests that sometimes water is beneficial in this condition. For practical purposes it appears wise to allow patients with heart failure to drink as much water as they please, provided the intake of sodium chloride (and other sodium salts) is carefully limited.

Compared to the amount of salt in the diets used in this study, the amount in the usual "salt-free" or "cardiac" diet is relatively high. An ordinary ward diet to which no extra salt and no salty foods have been added contains approximately 4.0 Gm. of sodium chloride; one cooked without salt contains 2.0 to 3.0 Gm. One gram of salt is present, for example, in an average serving of lamb, beets, and carrots, or in 800 c.c. of milk. When attention is not paid to the kind of food, as well as to the amount, the salt content may mount with surprisingly rapidity. Since it has been shown that some patients may gain weight when taking 2.0 Gm. and remain at the same weight when taking 1.0 Gm. of salt in twenty-four hours, the kind of food given in the treatment of this type of edema assumes importance. The beneficial effects of the Karell diet (800 c.c. of milk in twenty-four hours) may be due to the low content of fluid and of food, but especially to the fact that the salt content is also reduced to 1.0 Gm.

Few complaints were made about these diets when the food was properly seasoned. Patients were able to take them at home with less hardship than would be caused by the restriction of fluids.

This method for the control of edema merely removes or limits at the source one of the factors which is responsible for the accumulation of

extracellular fluid. The usual measures must also be employed to promote diuresis and to prevent reaccumulation of edema. But edema in congestive heart failure may often be kept in abeyance for considerable periods by rigid restriction of the amount of sodium chloride in the diet.

## SUMMARY

1. Twenty-three patients who were suffering from congestive heart failure were studied with a view to learning the relative importance of sodium chloride and water with respect to the accumulation and disappearance of edema.

2. The restriction of salt to a level below the output in the urine always resulted in a decrease in the amount of edema. Usually, a diet containing as little as 1.0 Gm. of salt in twenty-four hours was sufficient to cause diuresis or a cessation in the accumulation of edema, but the salt content of the ordinary "salt-free" diet was not low enough.

3. When the intake of salt was sufficiently restricted, the amount of fluid taken did not usually affect the edema.

4. Occasionally diuresis was observed to increase when the patient was taking plenty of fluids, and to decrease when fluids were rigidly restricted.

5. When renal insufficiency accompanied heart failure, a high intake of fluids resulted in symptoms similar to those of "water intoxication."

6. These studies suggest that restriction of salt is important in the control of the edema of congestive heart failure, but that the restriction of fluids is of little value.

## REFERENCES

1. Mackenzie, J.: Diseases of the Heart, Ed. 3, London, 1913, Oxford University Press.
   Lewis, T.: Diseases of the Heart, New York, 1936, The Macmillan Co.
   White, P. D.: Heart Disease, New York, 1935, The Macmillan Co.
2. Fishberg, A. M.: Heart Failure, New York, 1937, The Macmillan Co.
   Harrison, T. R.: Failure of the Circulation, Baltimore, 1935, Williams and Wilkins Co.
   Osborne, D. T., and Fishbein, M.: The Handbook of Therapy, Ed. 9, Chicago, 1933, American Medical Association.
3. Baird, M. M., and Haldane, G. B. S.: Salt and Water Elimination in Man, J. Physiol. **56**: 259, 1922.
4. Sherman, H. C.: Chemistry of Food and Nutrition, Ed. 5, New York, 1938, The Macmillan Co.
5. Peters, J. P.: Body Water: The Exchange of Fluids in Man, Springfield, Ill., 1935, C. C Thomas.
6. Adolph, E. F.: The Metabolism and Distribution of Water in Body and Tissues, Physiol. Rev. **13**: 336, 1933.
7. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Vol. I. Interpretations, p. 753, Baltimore, 1931, Williams and Wilkins Co.
8. Marshall, E. K., Jr.: The Influence of Diuresis on the Elimination of Urea, Creatinine and Chlorides, J. Pharm. Exper. Therap. **16**: 161, 1921.
9. Newburgh, L. H.: Personal communication.
10. Schemm, F. R.: Personal communication.

# THE PRODUCTION AND STUDY OF CARDIAC FAILURE IN THIAMIN-DEFICIENT DOGS

ROY L. SWANK, M.D., RENO R. PORTER, M.D., AND
ANDREW YEOMANS, M.D.
BOSTON, MASS.

ALTHOUGH recent studies indicate that cardiac failure may be produced in man by a deficiency of vitamin $B_1$,[1-8] the experimental production and study of this condition in animals has apparently been undertaken by few investigators. McCarrison[9] and Findlay[10] noted hydropericardium in many of their vitamin $B_1$-deficient pigeons, and studies on thiamin-deficient pigeons[11] and rats[12] have shown that the electrocardiograms become abnormal. These and many other similar investigations[13-16] have revealed bradycardia. However, other studies[17-19] have indicated that the bradycardia was the result, in large part, of starvation.*

In a recent study[20] it was found that, in thiamin-deficient dogs, tachycardia and abnormal electrocardiograms frequently appeared. These dogs became very markedly emaciated and had severe paralysis, both flaccid and spastic. At their post-mortem examinations[21] the right auricle and ventricle were found to be dilated, and the left ventricle in apparent contraction. Histologic examination of the myocardium revealed edema, perinuclear vacuolization, increase in the longitudinal striations, decrease in the cross striations, and hyalinization of many cardiac muscle fibers, and, in places, marked interstitial cellular infiltration was noted. In no instance was cardiac failure observed.

Another study, on pigeons,[22] has shown that hydropericardium, edema and engorgement of the lungs, engorgement of the liver, and peripheral edema can be produced in a large percentage of the birds by feeding them a diet partially deficient in thiamin, provided the caloric intake is sufficient to prevent a significant loss of weight. These pigeons developed tachycardia and abnormal electrocardiograms, and histologic study of the myocardium revealed scattered areas of focal necrosis.

To ascertain whether these phenomena are in fact due to failure of the myocardium, we have produced a similar state in the dog for more detailed studies. The method by which cardiac failure was produced in six dogs by feeding them a diet deficient in thiamin, together with pathologic observations, will be presented in the present paper. Physiologic ob-

From the Departments of Medicine and Pathology, Harvard Medical School, and the Medical Clinic of the Peter Bent Brigham Hospital, Boston.

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servations, using methods to be described separately,[23] will be presented as well, but in smaller numbers, because the symptoms of cardiac failure were followed so soon by death that few such studies were possible.

## MATERIALS AND METHODS

Young, normal, adult, female dogs were used. They were individually caged and fed the following experimental diet, which is deficient in thiamin:

| | |
|---|---|
| Casein (crude) | 180. |
| Cod liver oil | 40. |
| Peanut oil | 40. |
| Corn starch | 620. |
| Salt mixture | 20. |
| Autoclaved yeast | 50. |

This diet (15 to 18 Gm. per kilogram of body weight) was consumed voluntarily for ten to fourteen days, but thereafter, because of anorexia, was mixed with an equal weight of water and introduced into the dog's stomach by tube. Supplemental feedings of thiamin (betabione, Merck) were given either intramuscularly or orally with the day's ration. Many dogs vomited; two dogs which retained most of each day's ration were given only small daily supplements of thiamin (25 micrograms), and were allowed to develop acute thiamin deficiency. Ten others were made chronically deficient in thiamin, as follows: After a preliminary, rapid depletion period of approximately ten to fourteen days, during which no thiamin was added to the day's ration, each dog vomited. When this had occurred on two successive days, 0.3 to 0.6 microgram of thiamin per gram of the experimental diet (depending upon how much was needed to prevent a recurrence of vomiting) was added to the daily ration (preferably), or given intramuscularly. This regimen was followed for a period of four to twelve weeks, during which time the thiamin stored in the body was slowly used up. In some instances the administration of thiamin was then discontinued or the dose was reduced to approximately 0.2 microgram per gram of experimental diet, in which cases signs of cardiac failure or death usually appeared within three to five days. In others in which the reduction in thiamin was less marked (to 0.4 microgram per gram of diet), the symptoms of failure appeared less acutely, or, for reasons to be discussed later, failed to appear.

For the purpose of control, two dogs were starved by giving them approximately 7 Gm. of the experimental diet per kilogram of their original weight, plus an intramuscular injection of 100 micrograms of thiamin each day. These dogs lost approximately 30 per cent of their original weight, but showed no evidences of thiamin deficiency (anorexia, paresis, or dyspnea). No further mention of these experiments will be made. Two other dogs were utilized to ascertain the amount of thiamin necessary to prevent vomiting or other signs of thiamin deficiency in chronically deficient animals.

## RESULTS

*Acutely Deficient Dogs.*—Dogs 4 and 5 became deficient acutely. They vomited after consuming the experimental diet for twelve and seven days, respectively, and thereafter, to prevent further vomiting, received 25 micrograms of thiamin intramuscularly each day. Ataxia became apparent on the twenty-fourth and nineteenth days, respectively, when both dogs had lost 12 per cent of their original weight. One day later Dog 5 was found to have opisthotonus and extensor rigidity of the ex-

tremities. This was relieved in less than one hour by an intramuscular injection of 200 micrograms of thiamin.

In these and other (chronically deficient) dogs, ataxia was noticed first in the hind legs, later in the forelegs. It was characterized by a wide or straddle gait, misplacing of the feet, staggering, and a marked tendency to walk on the dorsum of the paws. Unless adequate amounts of thiamin were administered or the food intake greatly reduced, the ataxia became very much worse, a variable amount of spasticity of the extremities appeared, and in a few days there ensued a paralysis which was so severe that the animals were unable to stand or walk. This severe paralysis was due no doubt to motor as well as to sensory (proprioceptive) impairment, for the animals were unable to support their own weight. In a few cases the muscles of the neck also became involved, and the animals had difficulty in holding up their heads. Mild ataxia was abolished in seven to fourteen days by thiamin, but no attempt was made to restore to normal a dog that had severe paralysis. No evidences of cardiac failure were observed in the two acutely deficient dogs, and, as will be shown, paralysis (also starvation) tended to prevent the appearance of cardiac failure in the chronically deficient dogs. A similar observation on human patients was made by Keefer.[3]

*Chronically Deficient Dogs.—(a) General Consideration:* On the dietary regimen, which was partially deficient in thiamin, seven dogs developed sudden cardiac failure, principally of the left ventricle, and five of them died in a very few hours. Two of these were observed a short time before they died and showed labored breathing (not panting), pulmonary râles, cyanosis of mucous membranes, and poorly filled peripheral veins (as judged by the difficulty with which they were entered for the purpose of withdrawing blood). The other three were found dead in their cages. In no instance was dependent edema or an increase in peripheral venous pressure due to cardiac failure noted; all evidences pointed to failure of the *left* ventricle. Three of the dogs with cardiac failure developed mild ataxia very early in the experiment and were restored nearly to normal by a slight increase in the intake of thiamin, although this was still not sufficient to prevent the development of cardiac failure. Two other dogs became moderately paralyzed, and the last two dogs exhibited no evidences of paralysis at any time.

Four other dogs failed to exhibit any evidences of cardiac failure. One of these showed no signs of thiamin deficiency at all, presumably because of coprophagy; one other showed only slight paralysis and was suspected of coprophagy; and two others became very emaciated and paralyzed. In both dogs and pigeons,[22] emaciation and severe paralysis definitely delayed or prevented the development of cardiac failure.

In dogs with chronic thiamin deficiency an infusion with 10 per cent glucose in saline was followed in twelve to twenty-four hours by the

appearance of leg weakness (two cases) or cardiac failure (one case). Because of the apparent cause and effect relationship of the injection of glucose and the appearance or exacerbation of symptoms of thiamin deficiency, the use of this infusion fluid was abandoned.

*(b) Pathologic Observations:* Generally similar gross pathologic changes were found in all thiamin-deficient dogs that died from cardiac failure. There was frothy serosanguineous exudate in the trachea and bronchi; the lungs were purple to red in color, especially in dependent parts; and much frothy fluid could be expressed from them. Each pleural cavity contained from a few cubic centimeters to 150 c.c. of bloody fluid. The liver and kidneys were slightly engorged with blood

Fig. 1.—Section from cardiac muscle of a dog that died from cardiac failure. Note the area of necrosis, infiltrated with polymorphonuclear leucocytes, and the normal appearing muscle fibers at the periphery of the lesion (fixed in Zenker's-acetic acid solution and stained by eosin and methylene blue).

in two cases and normal in the others. The left ventricle and auricle were markedly dilated. All of the heart valves were normal grossly. Histologic study revealed some general shrinkage and pale indistinct staining of the muscle fibers in all the hearts. In three cases, small

scattered areas of myocardial necrosis were observed, many of which were infiltrated with polymorphonuclear leucocytes (Fig. 1). Histologic study of the lungs in all cases revealed edema and congestion (Fig. 2).

With the exception of the contracted left ventricle, which was also observed in dogs by Porto and De Soldati,[21] these abnormalities are compatible with left ventricular failure. The explanation for this apparent discrepancy is not known, but it may be pointed out that rigor mortis develops very soon after death in severely deficient pigeons, and that a

Fig. 2.—Section of lung from the same animal. Note the engorged capillaries and the pink staining edema fluid in the alveoli and bronchiole (fixed in Zenker's acetic acid solution and stained by eosin and methylene blue).

contracted heart is frequently found in pigeons that have died from cardiac failure.[22] It is quite possible that this contraction of the heart of the dog and pigeon occurs after death, for recent studies on man by Dr. Gustave Nylin* indicate that this is possible.

*Personal communication. This investigator found that the volume of a greatly enlarged heart could become reduced to half its pre-mortem size a few hours after death. The cardiac volume was computed from roentgenologic studies made before and after death, and the post-mortem volume was confirmed directly at autopsy.

*(c) Physiologic Observations:* Although five dogs died from cardiac failure, and a large number of *infusion tests** were performed on thiamin-deficient dogs that were vomiting or paralyzed, in only three instances were we able to demonstrate that the functional reserve (as measured by the infusion test) was diminished. In three other dogs (two died, and one recovered after thiamin administration) cardiac failure developed so rapidly that detailed studies could not be made, although the animals were observed. This testifies to the difficulty of producing and controlling cardiac failure once it has appeared. However, in one dog (Dog 11) significant circulatory and electrocardiographic observations during cardiac failure were recorded, and these will now be described. Electrocardiograms were recorded on one other dog with dyspnea and pulmonary edema, and they will be mentioned later.

Dog 11 (weight 14.6 kg.) received 350 and, later, 300 Gm. of the experimental diet, plus 225 and, later, 150 micrograms of thiamin by tube daily for twelve weeks. The ration was then reduced to 225 Gm. and the thiamin to 75 micrograms; two days later labored breathing appeared (made worse by the slightest exertion), and pulmonary râles developed. Electrocardiographic studies at this time showed definite elevation of the S-T segment in all leads (Fig. 4, Plate I) and tachycardia (Chart I). Fifteen hundred micrograms of thiamin were given intravenously, and thirty minutes later the dyspnea had disappeared and normal activity was resumed. The deficient diet was continued, and fifteen days later vomiting recurred; thiamin (75 micrograms daily) was then added to the ration again. Two days later, routine morning electrocardiograms revealed once more an elevation of the S-T segment in all leads (Fig. 9, Plate II). As dyspnea at rest was not yet evident, and the general condition of the dog was good, she was anesthetized with chloralose and prepared for an infusion test. The basal cardiac output was found to be 3.71 liters per minute, and an infusion with normal saline at a speed of 57 c.c. per minute was administered (Chart II). Such an infusion had been easily handled by this dog on many previous occasions, and at this time, except for a greater rise in the venous pressure, the response was normal. Ten minutes after the infusion ended, and while the venous pressure was dropping normally, dyspnea appeared, accompanied by pulmonary râles. Blood was drawn immediately from the right side of the heart and femoral artery to ascertain the cardiac output, which was found to be 3.10 liters per minute. Since in normal dogs the cardiac output ten minutes after completion of an infusion was always double or nearly double their basal cardiac output, and since this dog's basal cardiac output on this occasion was 3.71 liters per minute, this was a

*This test has been described in a paper to be published.[28] In carrying out this test, fluid was administered intravenously, in a known volume, and at a constant rate, and its effect estimated by observing the venous pressure, cardiac output, and pulse rate. The changes which occurred in these measurements, during such an infusion, gave an indication of the heart's ability to handle the increased "load," and in so doing gave an estimate of the functional reserve of the myocardium.

Fig. 3.

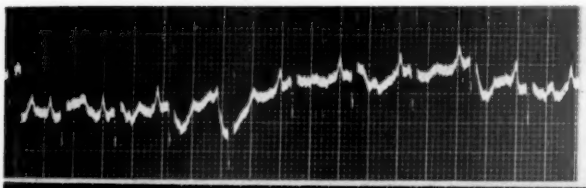

Fig. 4.

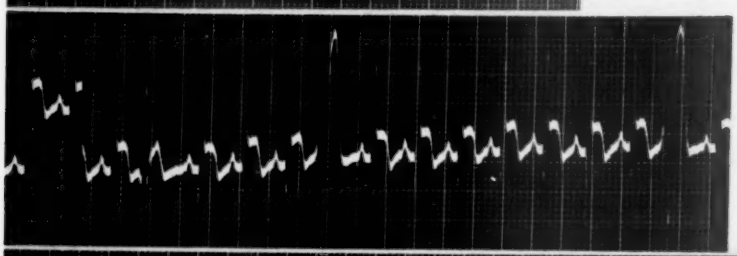

Fig. 5.

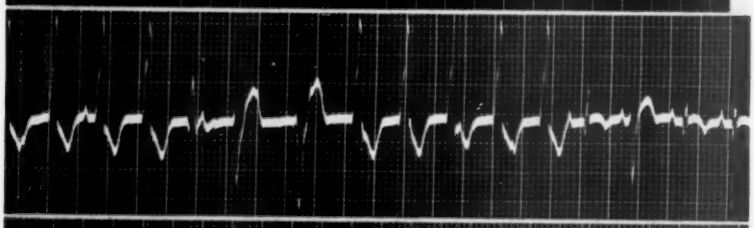

Fig. 6.

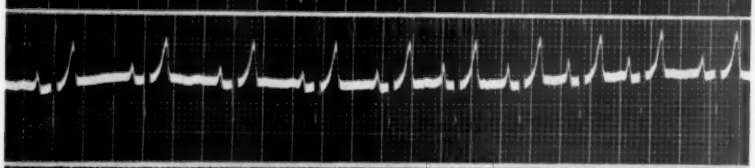

Fig. 7.

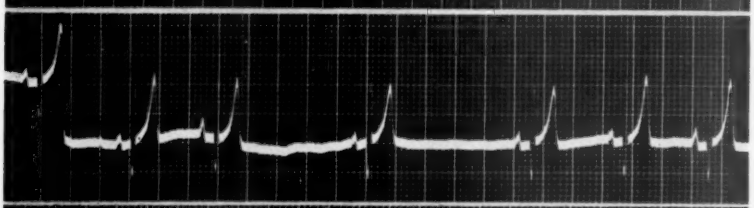

Fig. 8.

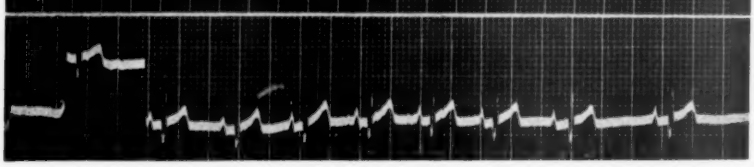

Plate I.—Series of Lead II electrocardiograms from Dog 11 during and between three attacks of cardiac failure. The daily basal heart rate during this period is shown in Chart II.

Fig. 3.—Normal control record taken before Dog 11 was placed on the experimental diet.

Fig. 4.—(June 13.) During first period of failure; note tachycardia (rate 210), marked change in the T waves, and extrasystoles (1,500 micrograms of thiamin were given intravenously immediately after this record was taken).

Fig. 5.—(June 15.) Note runs of ventricular extrasystoles (rate 180).

Fig. 6.—(June 18.) Normal rhythm; note elevated T waves (rate 150).

Fig. 7.—(June 23.) Normal rhythm; note elevated T waves (rate 80).

Fig. 8.—(June 28.) Apparently the cardiac musculature is becoming deficient again; note tachycardia (rate 135) and beginning changes in T waves.

low output. Thiamin (500 micrograms) was given intravenously, and in ninety minutes the dyspnea and pulmonary edema had practically disappeared and the S-T segment of the electrocardiograms had returned nearly to normal (Fig. 13, Plate II). Dog 11 continued to receive the deficient diet and fourteen days later was found dead in her cage. Her post-mortem weight was 14.2 kg., so that she lost only 0.4 kg. while receiving the thiamin-deficient diet.

Chart I shows the daily basal pulse rate of Dog 11 from the first attack of cardiac failure until death. Each period of failure was accompanied by tachycardia, which appeared several days before either dyspnea or abnormalities in the electrocardiograms were noted. When thiamin was given, the cardiac rate decreased gradually to normal during a period of several days. Preceding the onset of cardiac failure by two days,

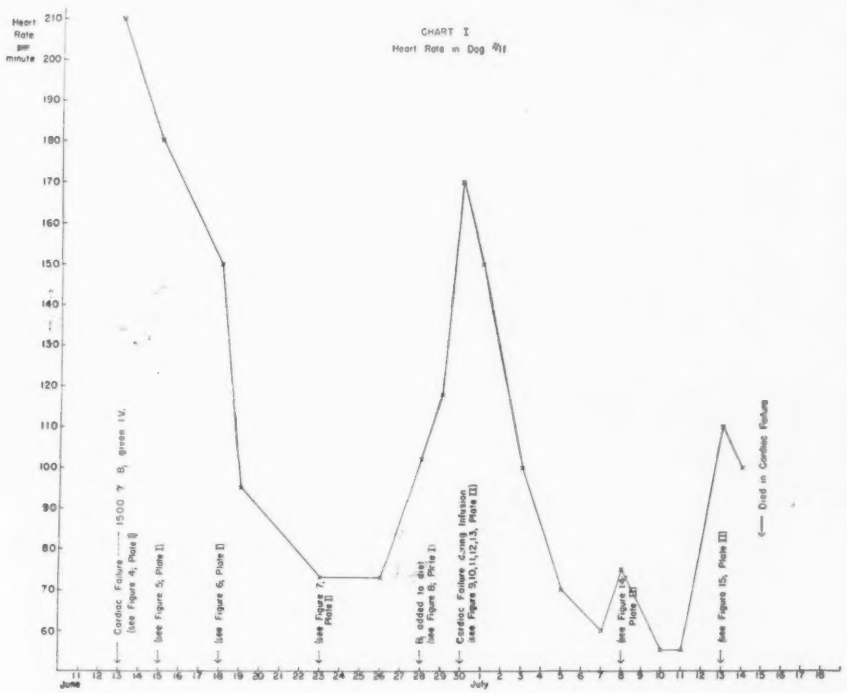


Chart I.—This chart shows the daily basal pulse rate of Dog 11 from the first attack of cardiac failure until her death. These cardiac rates were obtained by auscultation after the dog had rested for thirty minutes and was quiet and calm. The days on which the electrocardiograms in Plates I and II were taken are indicated in the chart.

slight but definite abnormalities were noted in the electrocardiograms (Fig. 8, Plate I; and Fig. 15, Plate II). With the appearance of dyspnea and pulmonary rales these changes became greater (Fig. 4, Plate I; and Fig. 9, Plate II). After thiamin was administered, the electrocardiographic complexes returned nearly to normal in about ninety minutes (Fig. 13, Plate II), but the dominant rhythm was then

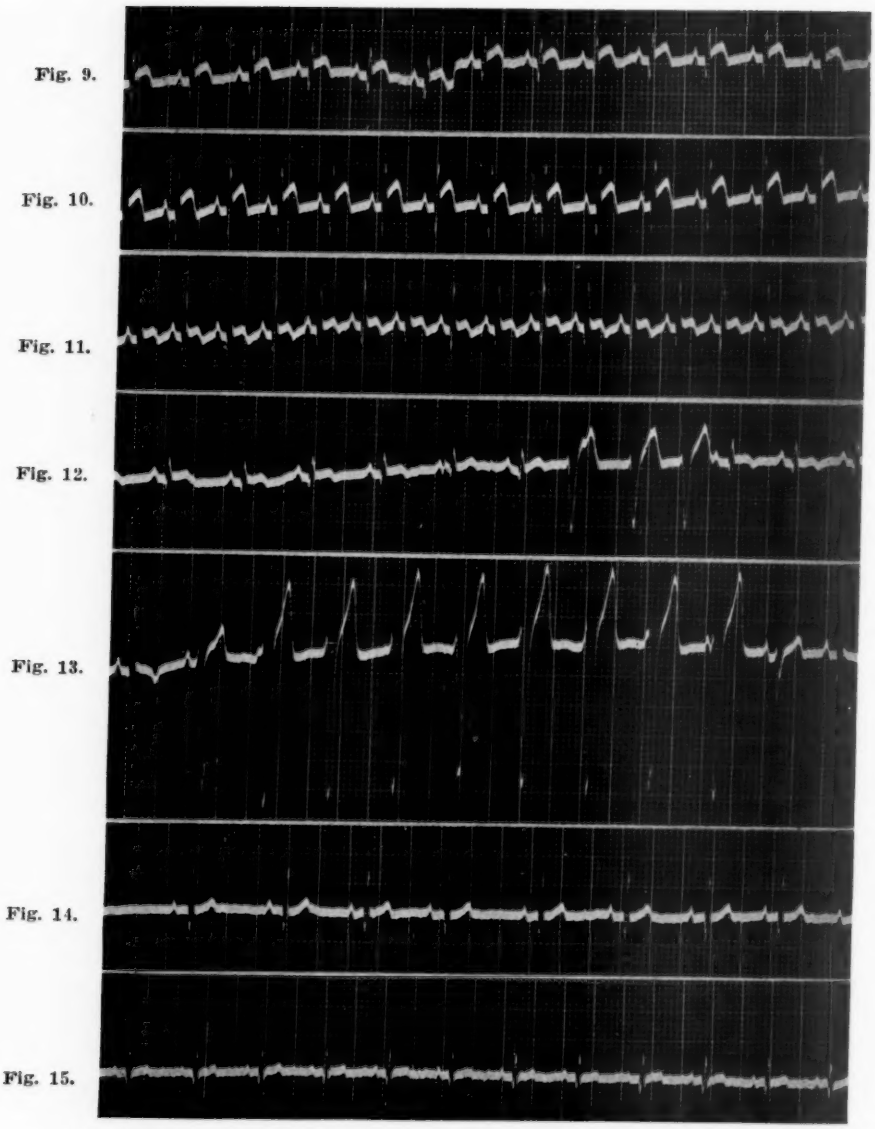

Fig. 9.

Fig. 10.

Fig. 11.

Fig. 12.

Fig. 13.

Fig. 14.

Fig. 15.

Fig. 9.—(June 30.) Dyspnea on effort present; note increased cardiac rate (165) and elevation of the S-T segment.

Fig. 10.—(June 30; two hours later.) Dyspnea and pulmonary râles present after conclusion of infusion test. Note T waves.

Fig. 11.—(June 30; ten minutes after thiamin was given intravenously.) Note return of T waves toward normal.

Fig. 12.—(June 30; thirty-five minutes later.) Cardiac rate slower (rate 150); note further changes in the T waves and ventricular extrasystoles.

Fig. 13.—(June 30; ninety minutes after thiamin was given.) Note the T waves and frequent ventricular extrasystoles.

Fig. 14.—(July 8.) Normal appearing complexes.

Fig. 15.—(July 13.) Note the very slight abnormalities in the electrocardiograms and tachycardia. Two days later this dog was found dead in her cage from cardiac failure.

disturbed by numerous extrasystoles which were present for three to four days. Later during the period of recovery the T waves became elevated to a height of 1 cm. (Fig. 7, Plate I).

The pathologic changes in Dog 11 are of especial interest. In addition to marked pulmonary edema and congestion, and a right-sided hydrothorax of 150 c.c. and left-sided hydrothorax of 50 c.c., there were some congestion of the liver and kidneys and edema of the posterior abdominal wall. The right auricle and ventricle were dilated, and the left ventricle was normal in size. Grossly, the heart muscle appeared pale, but otherwise normal, and the endocardium and pericardium appeared normal. Histologically, the myocardium revealed two distinct types of lesions. Small areas of focal necrosis (some with inflammatory cell infiltration) were scattered throughout the myocardium; these were similar to those described before, and illustrated in Fig. 1. In addition, there were other

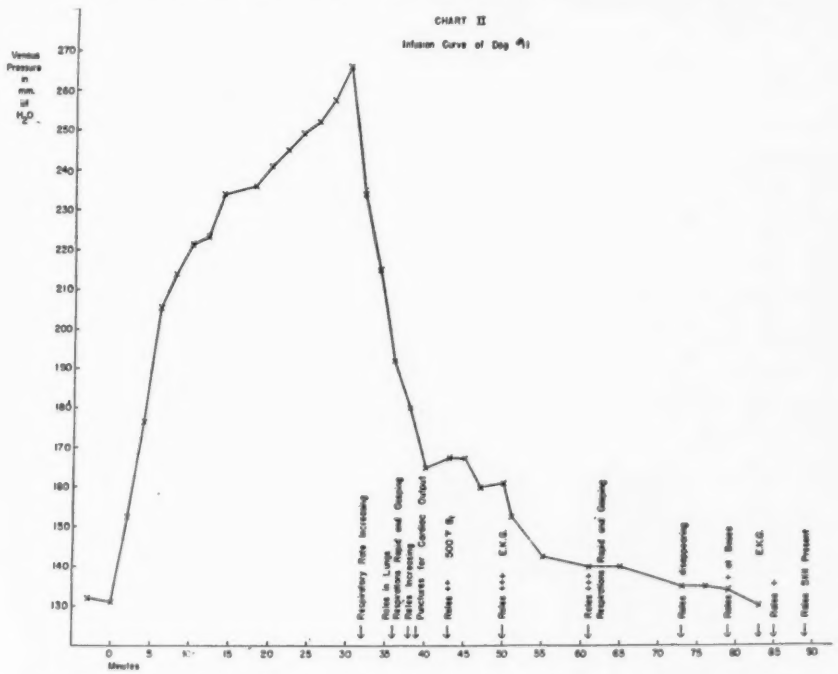


Chart II.—Chart of the infusion curve of Dog 11 on June 30, indicating the time relationship between appearance of râles in the lungs and completion of the infusion. Venous pressure measurements were made with the zero point of the manometer at the skin of the dog's back. The infusion curve rose at a constant rate for exactly thirty minutes, beginning at zero minutes.

focal lesions which appeared to be definitely older. They consisted of small areas of loose connective tissue from which myocardial fibers were obviously absent. These lesions were generalized and were of about the same size as the areas of focal necrosis. Although these focal lesions were seen in every microscopic field, by far the majority of muscle fibers appeared entirely normal.

*(d) Additional Observations:* In one of the other dogs with dyspnea and pulmonary edema (râles), electrocardiographic studies revealed definite, although moderate, changes in the myocardial action potentials. The Q waves in Lead I disappeared and in Lead III became very prominent, and the T waves in Lead I became more prominent and elevated and in Leads II and III inverted. These changes were accompanied by a tachycardia of 110, 135, and 120 (three observations within two hours). General improvement, which appeared to start spontaneously and was hastened by an intravenous injection of thiamin, was accompanied by a marked reduction in the cardiac rate and a very rapid return of the electrocardiogram to normal. In another animal, subcutaneous edema was observed in all extremities without other evidence of circulatory embarrassment or abnormalities in the electrocardiogram. This probably was not cardiac edema, but may have represented some other disorder due to thiamin deficiency.

## DISCUSSION

The means by which cardiac failure can be produced in thiamin-deficient pigeons have been outlined and discussed elsewhere.[22] The same general principles of dietary management produce a similar state in the dog. When a thiamin-deficient ration is consumed voluntarily by dogs, anorexia and a consequent, marked emaciation usually result.[20, 24] The animals may consume the deficient diet for two or three months before they develop paralysis, and they rarely (if ever) show evidences of cardiac failure. If the animals are made acutely deficient by tube feeding and small supplements of thiamin, only an insignificant loss of weight occurs (approximately 10 per cent); ataxia of the hind legs appears in about twenty-one days and becomes very severe a few days later if thiamin is not administered in large amounts. In such animals opisthotonus and extensor rigidity may develop. This has also been observed in cats by Odom and McEachern.* In acutely deficient dogs and pigeons, dyspnea, pulmonary râles, and post-mortem evidences of cardiac failure fail to appear, although a few acutely deficient pigeons with opisthotonus have exhibited minor changes in their electrocardiograms.[22]

To assure the production of cardiac failure, it is necessary, first, to deplete the animal's reserve of thiamin slowly by feeding it on a diet which is only slightly deficient in thiamin. According to our maintenance requirement studies, the practical thiamin requirement of dogs that consumed our experimental diet was about 60 micrograms (intra-

*Personal communication. These investigators found that tube-fed cats developed paralysis from thiamin deficiency in approximately three weeks. Although considerable weight loss occurred, three of their animals developed convulsive attacks consisting of opisthotonus and extensor rigidity of the extremities, and frequent clonic movements of all extremities. These attacks were quickly alleviated by thiamin.

muscularly) per 100 Gm. of diet,* which figure agrees favorably with that given by Arnold and Elvehjem.[25] Thus, if, subsequent to vomiting, 60 micrograms of thiamin, or less (40 micrograms), are given orally with every 100 Gm. of diet, a gradual depletion of the thiamin reserve results. When a dog becomes accustomed to tube feeding, the thiamin can be gradually reduced to 30 or even 20 micrograms per 100 Gm. of diet, but, if vomiting recurs or paralysis develops, the thiamin dosage should be increased. Mild ataxia in both dogs and pigeons frequently improved rapidly, and normal gait was restored when the thiamin dosage was increased slightly, i.e., from 30 to 40 or 50 micrograms per 100 Gm. of diet (dogs), even though the diet was still deficient in thiamin, and cardiac failure developed. In order to be sure of stopping the vomiting or increase of paralysis, it was found expedient, when paralysis appeared, to give one intramuscular injection of 100 or 200 micrograms of thiamin. In addition, the daily oral dosage of thiamin was increased slightly, depending upon the severity and acuteness of the paralysis.

It is important to avoid the development of severe paralysis or of a greater than 10 per cent loss of weight, for either or both tend to prevent the appearance of cardiac failure. Keefer[3] observed that, in patients with beriberi, paralysis tended to delay or prevent the onset of heart failure. It is quite likely that these two factors prevented the development of cardiac failure in De Soldati's dogs,[20] although tachycardia and abnormal electrocardiograms were noted ante mortem, and evidences of myocardial changes were observed post mortem. Perhaps emaciation and inactivity caused by paralysis reduce the work of the heart sufficiently to compensate for its impaired efficiency.

Several variable factors which may delay or prevent the appearance of thiamin deficiency in the dog are vomiting, coprophagy, and a high and variable thiamin content of yeast. As the thiamin requirement becomes reduced in proportion to the amount of the day's ration which is vomited or not consumed,[26, 27] it is possible by vomiting to reduce the thiamin requirement below the amount that is being administered intramuscularly. This complication can be minimized by mixing the thiamin with the day's ration. A second cause for failure, coprophagy,[28, 29] was suspected but never directly observed in one dog that received the experimental diet and no thiamin for six months without becoming deficient, and in another in which the onset of the deficiency was delayed. The thiamin content of different samples of yeast, all of which had been autoclaved in an alkaline medium at a pressure of 20 pounds for six hours, was found to vary significantly. This made it very difficult to know how much thiamin to add to the diet, but the problem was partially solved by reducing the yeast content of the diet from approx-

*This dosage of thiamin protected two chronically depleted dogs from vomiting, paralysis, and heart failure during a period of about eight weeks. It is quite possible that the true requirement is higher than this, because the tissue stores are able to supply some thiamin even though they are already very low. In this event some animals might become thiamin deficient on this dosage, especially if the experimental period were longer. It should be noted that our diet contained slightly more fat than the one used by Arnold and Elvehjem[25] in their experiments on dogs.

imately 10 per cent to 5 per cent, and by later utilizing a single source of this substance. On the other hand, glucose infusions, by greatly increasing the thiamin requirement, increased an already existing thiamin deficiency, with the result that paralysis or cardiac failure appeared suddenly.

Our limited observations on thiamin-deficient (but not starved) dogs indicate that the basal pulse rate may increase gradually during a period of four or five days preceding the appearance of definite cardiac failure. This is contrary to the observations of those investigators who believe that experimental thiamin deficiency in rats and pigeons is accompanied by bradycardia,[11-16] but in essential agreement with others who consider that this bradycardia is the result, in large part at least, of concomitant starvation.[17-19] It should be noted that tachycardia is almost invariably present in human beings with beriberi heart failure,[1-5] and that De Soldati[20] noted tachycardia in his thiamin-deficient dogs. In our dogs this tachycardia was accompanied (and possibly caused) by a gradually increasing nervousness, irritability, and increased tendency to vomit. Twenty-four to forty-eight hours before dyspnea at rest was evident, changes in the electrocardiogram appeared. These were similar to those described in rats and man by Weiss, et al.,[4, 5, 12] in man and pigeons by others,[1-3, 6, 11] and in the dog by De Soldati.[20] In one of our cases (Dog 11) the electrocardiographic changes consisted of depression and later a high take-off of the T waves in all leads, and in another dog less dramatic alterations were noted in the Q and T waves in Leads I and III. These changes were accompanied by dyspnea and pulmonary râles in both dogs, and in Dog 11 on a second occasion by a reduction in the cardiac reserve, as demonstrated by the infusion test. An intravenous injection of as little as 100 micrograms of thiamin caused the dyspnea and pulmonary râles to disappear rapidly, the electrocardiogram to approach normal in one to two hours, and the pulse rate to slow gradually to normal over a period of several days.

Electrocardiograms of thiamin-deficient pigeons which were allowed to lose very little or no weight have demonstrated very similar events.[22] The cardiac rate increased gradually during a period of several days before and while the electrocardiograms showed abnormalities. When thiamin was given intravenously (or intramuscularly), the electrocardiogram returned to normal in sixty to ninety minutes and the cardiac rate slowed to normal in twenty-four to forty-eight hours. When the food intake was reduced so that a rapid loss of weight occurred, the changes were similar to those observed in the dog.

The lesions observed in the cardiac musculature of these dogs (as also those reported in the pigeon[31] and man[4, 5, 7]) do not appear great enough to cause cardiac failure, especially in a few instances in which the areas of necrosis were very difficult to find microscopically. However, the very rapid return to normal of the electrocardiographic complexes after thiamin had been injected indicates that many more muscle fibers in the

heart were impaired functionally, and that these were capable of resuming normal function, as indicated by the electrocardiograms very soon after they were supplied with thiamin. It is possible that less severe myocardial changes, such as those observed by Porto and De Soldati, as well as many completely normal appearing myocardial fibers, were among those that were quickly restored to normal by thiamin. It seems reasonable to suggest, however, that repeated attacks of cardiac failure from thiamin deficiency, accompanied by necrosis of myocardial cells such as was observed in Dog 11, might result finally in a marked reduction of the functioning heart muscle, and its replacement by connective tissue. In such cases chronic cardiac failure might well develop, and probably would not be influenced so dramatically by the administration of thiamin. This is in agreement with a statement of Weiss[30] that, under thiamin therapy, the speed of recovery of patients with cardiac failure caused by beriberi is variable, and may require several weeks or longer.

The dyspnea and pulmonary râles ante mortem and pulmonary congestion and edema post mortem indicate that the cardiac failure in our thiamin-deficient dogs was primarily of the left ventricle. Had these animals survived longer (had failure been less acute), it is possible that obvious systemic congestion, with edema, similar to that observed in human beriberi, would have developed. The presence of bilateral hydrothorax, congestion of the liver, and edema of the posterior abdominal wall in Dog 11, and of smaller hydrothoraces with less hepatic congestion in several other dogs, indicated that some degree of right ventricular failure had already appeared.

## SUMMARY AND CONCLUSIONS

When dogs were fed a diet partially deficient in thiamin and a significant loss of weight was prevented by tube feeding, they developed dyspnea and pulmonary edema, and, at post-mortem examination, presented pulmonary congestion, edema, and other abnormalities which supported a diagnosis of cardiac failure, chiefly of the left ventricle. Histologic study of their myocardiums revealed many small areas of necrosis. Electrocardiographic studies revealed definite abnormalities in the electrical activity of the myocardium, and tachycardia just preceding and during such periods of cardiac failure. These changes disappeared quickly after the administration of thiamin. In one dog, circulatory studies showed that the cardiac reserve of thiamin-deficient dogs with dyspnea and pulmonary râles may be reduced. A more extensive consideration of circulatory studies in these and other dogs is to be reported elsewhere.[23]

## REFERENCES

1. Kepler, E. J.: Beriberi From a Diet of Raw Starch, J. A. M. A. **85**: 409, 1925.
2. Scott, L. C., and Herrmann, G. R.: Beriberi (''Maladie des Jambes'') in Louisiana, J. A. M. A. **90**: 2083, 1928.

3. Keefer, C. S.: The Beriberi Heart, Arch. Int. Med. **45:** 1, 1930.
4. Weiss, S., and Wilkins, R. W.: The Nature of the Cardiovascular Disturbances in Vitamin Deficiency States, Tr. A. Am. Physicians **51:** 341, 1936.
5. Weiss, S., and Wilkins, R. W.: The Nature of the Cardiovascular Disturbances in Nutritional Deficiency States (Beriberi), Ann. Int. Med. **11:** 104, 1937.
6. Inada, R.: Symptoms and Pathological Aspects of the Disturbances of the Circulatory System in Beriberi, Libman Anniversary, New York, 1932, International Press, vol. II, p. 577.
7. Aalsmeer, W. C., and Wenckebach, K. F.: Herz und Kreislauf bei der Beriberi-Krankheit, Wien. Arch. f. inn. Med. **16:** 193, 1929.
8. Goodhart, R., and Jolliffe, N.: The Role of Nutritional Deficiencies in the Production of Cardiovascular Disturbances in the Alcohol Addict, AM. HEART J. **15:** 569, 1938.
9. McCarrison, R.: The Pathogenesis of Deficiency Disease, Indian J. M. Research **7:** 279, 1919.
10. Findlay, G. M.: An Experimental Study of Avian Beriberi, J. Path. & Bact. **24:** 175, 1921.
11. Méhes, J., and Péter, F.: Die Wirkung des Digitoxins auf das Ekg der normalen und der an experimenteller Beriberi erkrankten Tauben, Arch. f. exper. Path. u. Pharmakol. **176:** 226, 1934.
12. Weiss, S., Haynes, F. W., and Zoll, P. M.: Electrocardiographic Manifestations and the Cardiac Effect of Drugs in Vitamin $B_1$ Deficiency in Rats, AM. HEART J. **15:** 206, 1938.
13. Carter, C. W., and Drury, A. N.: Heart Block in Rice-Fed Pigeons, J. Physiol. **68:** i, 1929.
14. Drury, A. N., Harris, L. J., and Maudsley, C.: Vitamin B Deficiency in the Rat. Bradycardia as a Distinctive Feature, Biochem. J. **24:** 1632, 1930.
15. Birch, T. W., and Harris, L. J.: Bradycardia in the Vitamin $B_1$-Deficient Rat and Its Rise in Vitamin B Determinations, Biochem. J. **28:** 602, 1934.
16. Baker, A. Z., and Wright, M. D.: A Survey of the Rat-Bradycardia Method of Estimating Vitamin $B_1$, Biochem. J. **33:** 1370, 1939.
17. Parade, G. W.: Vitamin B-Untersuchungen; zur Frage des Zusammenhanges zwischen Vitamin $B_1$-Mangel und Bradykardie, Ztschr. f. Vitaminforsch. **6:** 327, 1937.
18. Parade, G. W.: Vitamin B-Untersuchungen; Vitamin $B_1$-Mangel, Bradykardie und Temperatursturz, Ztschr. f. Vitaminforsch. **7:** 35, 1938.
19. MacDonald, D. G. H., and McHenry, E. W.: Studies on Rat Bradycardia, Am. J. Physiol. **128:** 608, 1940.
20. De Soldati, L.: Los trastornos circulatorios del perro en avitaminosis $B_1$. I: El pulso, la tensión arterial y el electrocardiograma, Rev. Soc. argent. de biol. **15:** 142, 1939.
21. Porto, J., and De Soldati, L.: Alteraciones microscópicas del corazón del perro en avitaminosis $B_1$, Rev. Soc. argent. de biol. **15:** 303, 1939.
22. Swank, R. L., and Bessey, O. A.: The Production and Study of Cardiac Failure in Thiamin Deficient Pigeons, J. Clin. Investigation, Abstract, 1940.
23. Observations on Certain Manifestations of Circulatory Congestion Produced in Dogs by Rapid Infusion. (Unpublished observations from this laboratory.)
24. Cowgill, G. R.: The Vitamin $B_1$ Requirement of Man, New Haven, 1934, Yale University Press.
25. Arnold, A., and Elvehjem, C. A.: Influence of the Composition of the Diet on the Thiamin Requirement of Dogs, Am. J. Physiol. **126:** 289, 1939.
26. Swank, R. L., and Bessey, O. A.: Avian Thiamin Deficiency. Characteristic Symptoms and Their Production. (To be published.)
27. Williams, R. R., and Spies, T. D.: Vitamin $B_1$ (Thiamin) and Its Use in Medicine, New York, 1938, The Macmillan Co.
28. Bliss, S.: Refection in the Rat, J. Nutrition **11:** 1, 1936.
29. Salaam, A. A., and Leong, P. C.: Synthesis of Vitamin $B_1$ by Intestinal Bacteria of the Rat, Biochem. J. **32:** 958, 1938.
30. Weiss, S.: The Application of Electrocardiography in the Detection of Avitaminosis $B_1$, Proc. Round Table on Nutrition and Public Health, 16th Ann. Conf. Milbank Memorial Fund, March 29-31, 1938, p. 82.
31. Swank, R. L.: Avian Thiamin Deficiency. A Correlation of the Pathology and Clinical Behavior, J. Exper. Med. **71:** 683, 1940.

# CHANGES IN THE RHYTHM OF THE HEART DURING RESECTION OF THE PERICARDIUM IN CHRONIC CONSTRICTIVE PERICARDITIS, AS RECORDED ELECTROCARDIOGRAPHICALLY

HAROLD J. STEWART, M.D., AND ROBERT L. BAILEY, JR., M.D.
NEW YORK, N. Y.

THAT resection of the pericardium in cases of chronic constrictive pericarditis may be safely performed has been demonstrated by Schmieden, et al.,[1, 2] Churchill,[3] Beck and Griswold,[4] Heuer, et al.,[5, 6, 7] and by Blalock, et al.[8, 9, 10] Heuer and Stewart[5] have recently reviewed the published data relating to the surgical treatment of this disease, and Stewart and Heuer[6, 7] and Burwell and Blalock[11] have studied the dynamics of the circulation in the presence of this lesion. It is of practical importance to know how the heart behaves during the resection of the closely attached pericardium.

Feil and Rossman[12] have reported the electrocardiographic changes during operation in twenty-four patients who were the subjects of cardiac anastomosis for the treatment of angina pectoris and coronary sclerosis, and in cases in which the pericardium was resected. Patients who were subjected to cardiac anastomosis showed electrocardiographic changes more frequently than those whose pericardiums were resected. Most of the abnormalities occurred during manipulation of the heart. The use of quinidine sulfate preoperatively in certain of the cases appeared to prevent the occurrence of arrhythmias. This impression could not be demonstrated conclusively by comparing the electrocardiograms of these patients with those of subjects who had not received quinidine. Mautz[13] and Beck and Mautz[14] applied local anesthetics to the surface of the heart in an attempt to reduce its surface irritability during cardiac surgical procedures. They found that applying a solution of procaine directly to the auricles and ventricles reduced the incidence of arrhythmias during operations on the heart in man. This measure was efficacious experimentally in dogs in converting auricular fibrillation to normal sinus rhythm, and also terminated ventricular fibrillation.

Feil and Rossman's[12] observations are the only records in the literature relating to changes in the cardiac rhythm during pericardial resection. We have had the occasion to make electrocardiograms during resection of the pericardium in the last six cases of chronic constrictive pericarditis in which we have used this method of treatment. We had gained the impression from observing the hearts of the other seven patients during operation that disturbances of rhythm were infrequent

From the New York Hospital and Department of Medicine, Cornell University Medical College, New York, N. Y.
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and of short duration. We wished, however, to ascertain with certainty the nature of the irregularities. These observations are now being reported. In five cases, J. P., C. G., G. S., E. B., and J. C., the operations were performed by Dr. George J. Heuer, as previously described,[5] and, in the other case, P. M., by Dr. W. D. Andrus. All patients had had the usual preoperative study and treatment.[5, 6, 7] The three standard leads of the electrocardiogram were taken after the patient had been placed on the operating table. This served as a control. Another electrocardiogram was taken after anesthesia had been induced by the use of open drop ether, and subsequent ones at frequent intervals throughout the operative procedure, namely, when the chest was opened, when dissection of the pericardium was started, and at frequent intervals during resection. A final record was made after the chest had been closed. From seven to twelve electrocardiograms were taken during each operation.

## OBSERVATIONS

J. P., History No. 155618, a man, aged 36 years, was admitted to hospital Nov. 4, 1938. He had suffered from dyspnea on exertion, swelling of the legs and abdomen, and palpitation, for eight years. There was no history of rheumatic fever, tuberculosis, or any other illness which might have been the etiologic factor in the production of chronic constrictive pericarditis. He presented the following signs and symptoms: dyspnea, cyanosis, massive edema of the legs, marked distention of the superficial veins, fluid in the right pleural cavity, marked enlargement of the liver, and marked ascites. The heart did not appear to be enlarged; there were no abnormal signs on auscultation. Auricular fibrillation prevailed. The blood pressure measured 108/68. The radial pulse was paradoxical. The venous pressure was elevated to 305 mm. of saline, and the arm-to-tongue circulation time (Decholin) was prolonged to 26.4 seconds. Roentgenograms of the heart did not show calcification of the pericardium; fluoroscopic examination of the heart showed diminished amplitude of the cardiac pulsations. On Feb. 14, 1939, when the signs and symptoms had been alleviated by medical treatment,[6] resection of the pericardium was performed. The pericardium was found to be markedly thickened, and the parietal pericardium was everywhere adherent to the surface of the heart. Calcification of the pericardium was not observed. Resection of the pericardium over the entire anterior surface of both ventricles and the apex of the heart was carried out by careful sharp and blunt dissection.

The preoperative electrocardiogram showed auricular fibrillation, with a ventricular rate of 90 per minute. The QRS complexes were low and slightly split. The T waves were diphasic in all leads. The patient had been well digitalized to keep the ventricular rate slow,[5, 6, 7] and the form of the T waves was in part a digitalis effect. The QRS conduction time was within normal limits, and there was no deviation of the electrical axis. An increase in the ventricular rate from 90 to 120 per minute was the only change in the electrocardiogram until pericardial resection was begun. At this time, ventricular premature contractions occurred. Both left and right ventricular premature contractions,* but more of the former, appeared while the pericardium covering the anterior surface of the left ventricle was being resected. Shortly after the resection of the pericardium from the anterior surface of the left ventricle had been started, there were two left ventricular premature contractions in succession; after this there were four left ventricular premature contractions in succession, forming a short run of ventricular parox-

*Old terminology.

ysmal tachycardia. When resection of the pericardium from the left ventricle had been partially completed, several right ventricular premature contractions were recorded. These occurred singly and in pairs, and appeared to arise from different foci. As resection over left ventricle neared completion, occasional left ventricular premature contractions occurred singly, and there was a series of five left ventricular contractions in succession, constituting a short run of ventricular paroxysmal tachycardia. A single right ventricular premature contraction appeared while the right ventricle was being uncovered, and a left ventricular premature contraction was recorded after resection had been completed. On comparing the records taken before and at the completion of the operation, the T waves in Lead I had increased slightly, and the QRS complexes in Lead II were decreased slightly, in amplitude. On the whole, however, the series of electrocardiograms showed no changes of significance except the ventricular premature contractions and the short runs of ventricular paroxysmal tachycardia.

C. G., History No. 97484, a white man, aged 33 years, was admitted to hospital May 20, 1939. He stated that he had suffered from dyspnea on exertion for twelve years and from a feeling of fullness in the epigastrium after exertion for seven years. He had never had orthopnea, edema, ascites, or precordial pain. There was no history of rheumatic fever, tuberculosis, or any other infection which might have been the etiologic factor in the production of chronic constrictive pericarditis. The patient presented the following signs and symptoms: cyanosis, distention of the superficial veins, fluid in the right pleural cavity, and enlargement of the liver. The heart did not appear to be enlarged, and no murmurs were heard. The rhythm was normal. The blood pressure measured 130/90. The radial pulse was paradoxical. A roentgenogram of the heart showed calcification of the pericardium. Fluoroscopic examination of the heart revealed diminished amplitude of the cardiac pulsations. The venous pressure was elevated to 123 mm. of $H_2O$, and the arm-to-tongue circulation time (Decholin) increased to 36.4 seconds. Resection of the pericardium was performed May 29, 1939. At operation, calcification of the pericardium was observed along both the right and left borders of the heart. The pericardium over the anterior surface of the heart was not calcified, but the parietal pericardium was adherent to the anterior surface of the heart. Resection of the pericardium over the anterior surface of the heart was carried out by blunt dissection.

The preoperative electrocardiogram showed normal sinus rhythm, with a heart rate of 110 per minute (Fig. 1). The P-R and QRS conduction times were within normal limits. There was slight deviation of the electrical axis to the right. The QRS complexes were slightly split in Leads I and II, and were low and split in Lead III. The T waves were positive in Leads I and II and diphasic in Lead III. The RS-T segments were slightly depressed in Leads II and III. Auricular premature contractions were present in all leads. During operation the heart rate increased, and varied between 120 and 160 per minute. The electrocardiogram which was taken during resection of the ribs showed a paroxysm of auricular fibrillation in Lead I, and, in Lead II, a run of auricular fibrillation, followed by two auricular premature contractions and then a run of auricular paroxysmal tachycardia. As the pleura was being opened, the transition from normal rhythm to auricular fibrillation was recorded in Lead I; Lead II showed auricular fibrillation, which was replaced by one auricular premature contraction and then auricular flutter, with a varying rate of ventricular response. A paroxysm of auricular fibrillation, followed by multiple auricular premature contractions, was recorded as resection of the pericardium from the left ventricle was begun. The record which was taken as the pericardium was being dissected from the right ventricle showed auricular fibrillation, followed by multiple auricular premature contractions and then normal rhythm in Lead I and auricular fibrillation in Lead II. A paroxysm of auricular fibrillation, followed by multiple auricular premature contractions, was recorded

as the pleura was being closed. The final record, taken as the muscle flaps were being closed, showed auricular fibrillation, followed by multiple auricular premature contractions and then another paroxysm of auricular fibrillation. Normal rhythm recurred later in the day and persisted. No ventricular premature contractions were recorded. The slight deviation of the electrical axis to the right disappeared after resection of the pericardium had been completed. The QRS complex in Lead I decreased in amplitude. The T waves varied in amplitude during the procedure, especially in Lead III, in which they changed from diphasic to negative, and finally to positive as the pericardium was being resected. The T waves in Lead I decreased slightly in amplitude, and, in Lead II, increased slightly in amplitude. In this case the changes which were recorded were an increase in the frequency of the auricular premature contractions and paroxysms of auricular fibrillation, auricular flutter, and auricular paroxysmal tachycardia.

G. S., History No. 232001, a white man, aged 52 years, was admitted to hospital May 25, 1939. At the age of 15 years he suffered from cough for six months, and during this period an opening in the skin over the suprasternal notch appeared, from which pus drained. At the age of 34 years he suffered from "double pneumonia," and was told at this time that his heart was enlarged and "irregular." He experienced no cardiac symptoms until he was 45 years of age, seven years before admission, when he began to suffer from swelling of the abdomen, which progressed steadily in severity. He had never had dyspnea, orthopnea, or edema. The patient presented the following signs and symptoms: slight cyanosis, marked distention of the superficial veins, fluid in both pleural cavities, enlargement of the liver, and marked ascites. The heart did not appear to be enlarged, and no murmurs were heard. Auricular fibrillation was present. The blood pressure

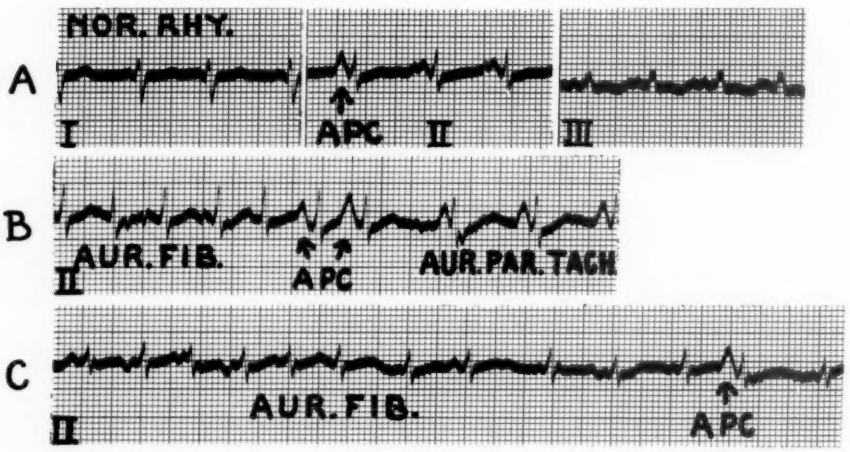


Fig. 1.—Electrocardiograms of C. G. *A* was taken before anesthesia was induced; normal rhythm (*Nor. Rhy.*) prevailed, and one auricular premature contraction (*APC*) was recorded in Lead II. *B* was taken during resection of the ribs, and shows paroxysmal auricular fibrillation (*Aur. Fib.*), followed by two auricular premature contractions (*APC*) and then a run of auricular paroxysmal tachycardia (*Aur. Par. Tachy.*), apparently from the same focus as the auricular premature contraction in Lead II, in *A*. *C* was taken after closure of the chest, as the muscle flaps were being sutured. There were recurrence of auricular fibrillation (*Aur. Fib.*) and one auricular premature contraction (*APC*). In this figure, as well as in Fig. 2, divisions of the ordinates equal 10-4 volts, and divisions of the abscissae equal 0.04 second. The electrocardiograms are reduced to three-quarters of their original size. The leads which are reproduced are indicated.

measured 112/74. The radial pulse was paradoxical. The venous pressure was 173 mm. of saline, and the arm-to-tongue circulation time was increased to 23.9 seconds (Decholin). Roentgenograms of the heart showed calcification of the pericardium. Fluoroscopic examination of the heart revealed diminished amplitude of the cardiac

pulsations. After suitable preoperative treatment, the thickened and partially calcified pericardium was resected from the anterior surface of the left and right ventricles.

The preoperative electrocardiogram showed auricular fibrillation, with a ventricular rate of 107 per minute and slight deviation of the electrical axis to the right (Fig. 2). The QRS conduction time was within normal limits. The QRS complexes in Lead I were split and small, in Leads II and III, slightly split. The T waves were positive in Lead I, diphasic in Lead II, and negative in Lead III, and the RS-T segments were slightly depressed in Leads II and III. The patient was receiving digitalis to keep the ventricular rate slow. Auricular fibrillation persisted during the operation, with a ventricular rate which varied between 80 and 100 per minute. The slight deviation of the electrical axis to the right disappeared after the ribs had been resected, but reappeared after the chest was closed. There was no appreciable change in the QRS complexes except for a slight decrease in their amplitude in Leads II and III after the pericardium had been opened. The T waves changed in form and amplitude during the procedure. The T wave in Lead I became negative after resection of the ribs, became more negative during resection of the pericardium, and then became less negative after the wound was closed. The T wave in Lead II showed little change. The T wave in Lead III became diphasic after the ribs had been resected and showed small variations in amplitude during the progress of the operation. A single ventricular premature contraction was recorded in Lead II as the pleura was being resected. As the pericardium was being resected from the right ventricle, a single ventricular premature contraction was recorded in Lead II; four right ventricular premature contractions in succession in Lead III formed a short run of ventricular paroxysmal tachycardia, followed by a single left ventricular premature contraction and then a single right ventricular premature contraction. A single right ventricular premature contraction was recorded as resection of the pericardium was completed.

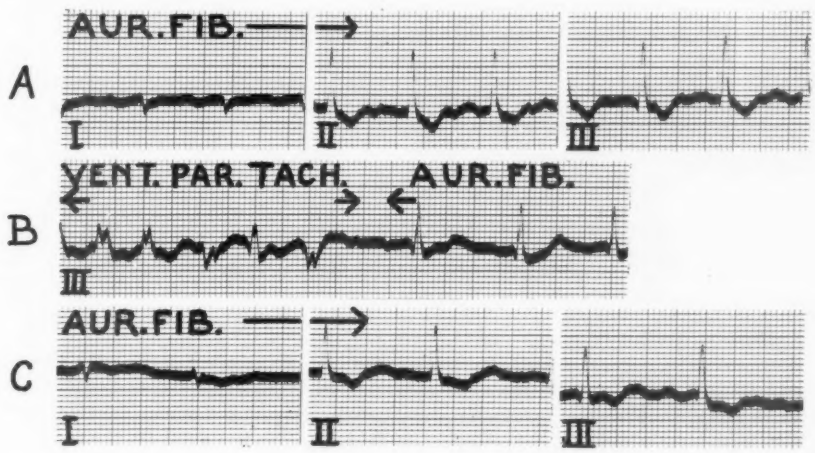


Fig. 2.—Electrocardiograms of G. S. *A* was taken before induction of anesthesia. Auricular fibrillation (*Aur. Fib.*) was present. *B*, taken during resection of the pericardium from the right ventricle, shows a run of ventricular paroxysmal tachycardia (*Vent. Par. Tachy.*), with reversion to auricular fibrillation (*Aur. Fib.*). *C*, taken after completion of the operation, shows persistence of auricular fibrillation (*Aur. Fib.*)

E. B., History No. 233623, a white man, aged 22 years, was admitted to hospital Sept. 19, 1939. Two years before, he had experienced weakness and dizziness on sudden exertion. Swelling of the abdomen and frequent attacks of vomiting soon appeared. About one and one-half years before admission, he began to suffer from

dyspnea on exertion, edema of the feet and legs, varicose veins of the legs, and cyanosis of lips, finger tips, and ears.

Examination showed cyanosis of the lips and nail beds, fluid in the left pleural cavity, distention of the superficial veins, enlargement of the liver (10 cm. below the right costal margin) and spleen (1 cm. below the left costal margin), edema of the legs and scrotum, and varicose veins of the legs. The heart was not enlarged, the rhythm was normal, the apex impulse was neither seen nor felt, the blood pressure was 114/88, and the pulse was paradoxical. The venous pressure was elevated to 186 mm. of saline, and the arm-to-tongue circulation time was prolonged to 25.0 seconds (Decholin). Roentgenographic and fluoroscopic examination did not reveal calcium in the pericardium; the cardiac pulsations were decreased. After suitable preoperative treatment, the thickened pericardium was resected from the anterior surface of the left and right ventricles.

The preoperative electrocardiogram showed normal sinus rhythm, with a rate of 100 per minute. The QRS complexes in Lead I were low and slightly split, the T waves were diphasic in Leads I and II and negative in Lead III, and the R-T segments were slightly depressed in all leads. The heart rate increased after the induction of anesthesia to 111 beats per minute, and tachycardia persisted throughout the procedure; the rate returned to 100 beats per minute after the chest had been closed. There were slight changes in the amplitude and contour of the T waves and slight variations in the R-T segments during the operation. After the induction of anesthesia, $T_1$ became positive instead of diphasic, and $T_3$ became slightly less negative. $T_3$ became diphasic after resection of the ribs. $T_2$ increased slightly in amplitude, and $T_3$ became less negative after resection of the pleura. After resection of the pericardium from the anterior surface of the right ventricle, $T_1$ again became diphasic and the R-T segment of Lead III rose to the isoelectric line. The R-T segment in Lead I returned to the isoelectric line, and the R-T segment of Lead III again became depressed after completion of the resection of the pericardium. After the chest was closed, $T_2$ and $T_3$ became slightly more negative. A comparison of the records taken before and after operation showed very little change. This patient had neither premature contractions nor other arrhythmias.

P. M., History No. 273718, a white man, aged 42 years, was admitted to hospital Aug. 8, 1940. He had suffered from swelling of the legs and abdomen, and dyspnea on exertion, intermittently for twelve years, and constantly during the two years before admission. He had had numerous respiratory infections. Two years before the onset of symptoms, he had a five months' illness which was diagnosed as "influenza." Swelling of the legs had been present during this illness. There was no history of rheumatic fever or chorea, or of exposure to tuberculosis. He presented the following signs and symptoms: dyspnea, venous engorgement, cyanosis, marked edema of the legs and abdominal wall, fluid in both pleural cavities, enlargement of the liver, and ascites. The heart did not appear to be enlarged on physical examination, and there was no abnormality of the heart sounds. Auricular fibrillation prevailed. The blood pressure measured 104/68. The radial pulse was paradoxical. The venous pressure was elevated to 160 mm. of saline, and the arm-to-tongue circulation time (Decholin) was prolonged to 19.5 sec. Roentgenograms of the heart showed calcification of the pericardium over the anterior surface of the heart. Fluoroscopic and kymographic examination revealed greatly diminished pulsations along the right border of the cardiac shadow. On Sept. 15, 1940, after he had been rendered free of fluid accumulations by medical treatment,[6] resection of the pericardium was performed. At operation the pericardium was found to be markedly thickened and partially calcified, and the parietal pericardium was adherent to the surface of the heart. Resection of the pericardium over the anterior surface of the heart was carried out by careful sharp and blunt dissection.

The preoperative electrocardiogram showed auricular fibrillation, with a ventricular rate of 110 per minute. The QRS conduction time was within normal limits. The QRS complexes were split, low, and varied in amplitude in Leads I, II, and III. The T waves were negative in Leads I, II, and III, and the R-T segments were slightly depressed in Leads I and II; these abnormalities were probably caused by the digitalis which the patient received to keep the ventricular rate slow. The ventricular rate increased after resection of the ribs, and tachycardia persisted throughout the procedure. There was no change in rhythm, electrical axis deviation, or in the form of the QRS complexes. The T waves in Lead II became diphasic instead of negative after resection of the pericardium over the left side of the heart had been completed, and then became negative again after resection over the right side of the heart had been completed. This patient showed no premature contractions at any time. A comparison of the records taken before and at the completion of operation showed no appreciable change in the form of the electrocardiogram.

J. C.,* History No. 290121, a white boy, aged 7 years, was admitted to hospital March 1, 1940. He had been in good health without symptoms until three months before admission, when he suffered from a respiratory infection associated with cough. He gained weight rapidly, became short of breath on exertion, and the abdomen increased in size. Three weeks after the onset he was admitted to a hospital, where abdominal paracentesis yielded one pint of fluid. He improved on a regimen of rest in bed and digitalis. He was discharged against advice after 48 days in the hospital. At home the fluid intake and activity were restricted, but the abdomen increased progressively in size and he continued to be short of breath. On admission to New York Hospital, the following signs were observed: slight cyanosis of the lips, enlarged tonsils, engorgement of the neck veins, flaring of the ribs, moderate enlargement of the heart to left and right, normal sinus rhythm (rate 108 per minute), a loud systolic murmur over the precordium, best heard in the third left intercostal space near the sternum, signs of free fluid in the left pleural cavity, signs of fluid in the peritoneal cavity, and enlargement of the liver (the edge extended three fingerbreadths below the right costal margin and was not tender). The blood pressure measured 86/65. The radial pulse was paradoxical. The arm-to-tongue circulation time (Decholin) was increased to twenty-one seconds, and the venous pressure measured 207 mm. of saline. On fluoroscopic and roentgenkymographic examination of the heart, pulsations were decreased except in the pulmonary conus region. After a suitable period of preoperative care, a thickened and partially calcified pericardium was resected from the anterior surface of the left and right ventricles.

The preoperative electrocardiogram showed normal sinus rhythm and sinus tachycardia, with a ventricular rate of 167 per minute. The P-R and QRS conduction times were within normal limits, there was no abnormal axis deviation, the QRS complexes were split and low in all leads, $T_{1, 2}$ were diphasic, and $T_3$ was negative. During operation the heart rate became somewhat slower; it varied between 140 and 150 per minute, but normal sinus rhythm persisted. The amplitude of the QRS complexes in Leads I and II varied slightly, but showed no appreciable change in form. This patient exhibited neither premature contractions nor other arrhythmias, nor was there any significant change in the form of the T waves and R-T segments during resection of the pericardium.

## DISCUSSION

The electrocardiograms in these six cases (Table I) showed premature contractions and paroxysms of abnormal rhythms as the most striking changes during pericardiectomy. Two patients who had auricular fibril-

*We wish to thank Dr. Elvira Ostlund for referring this patient to us.

TABLE I

CHANGES IN THE ELECTROCARDIOGRAMS DURING PERICARDIECTOMY

| CASE | RHYTHM PREVAILING BEFORE OPERATION | CHANGES IN RHYTHM DURING OPERATION | CHANGES IN ELECTRICAL AXIS DEVIATION | CHANGES IN T WAVES | CHANGES IN R-T SEGMENTS | CHANGES IN RATE |
|---|---|---|---|---|---|---|
| J. P. male 36 yr. | Auricular fibrillation | Vent. premature contractions; vent. paroxysmal tachycardia | none | $T_1$ increased slightly in amplitude | No significant change | Increased from 90 to 125 |
| C. G. male 33 yr. | Normal sinus rhythm with auricular premature contractions | Auric. premature contractions; auric. paroxysmal tachycardia; paroxysmal auric. fibrillation and paroxysmal auric. flutter | slight rt. axis deviation disappeared | $T_{1, 2}$ varied slightly in amplitude; $T_3$ became positive instead of diphasic | No significant change | Increased from 110 to 160 |
| G. S. male 52 yr. | Auricular fibrillation | Vent. premature contractions; vent. paroxysmal tachycardia | Slight rt. axis deviation disappeared and reappeared later at completion of the operation | $T_1$ became negative instead of positive; $T_3$ became diphasic instead of negative | No significant change | Decreased from 107 to 80. |
| E. B. male 22 yr. | Normal sinus rhythm | none | none | $T_1$ changed from diphasic to positive and back to diphasic; $T_3$ changed from negative to diphasic | $R\text{-}T_{1, 3}$ varied slightly | Increased from 100 to 111 |
| P. M. male 42 yr. | Auricular fibrillation | none | none | $T_2$ changed from negative to diphasic and back to negative | none | Increased from 110 to 130 |
| J. C. male 7 yr. | Normal sinus rhythm | none | none | none | none | Decreased from 167 to 140 |

lation showed ventricular premature contractions and short runs of ventricular paroxysmal tachycardia (J. P. and G. S.), and one patient with normal sinus rhythm showed auricular premature contractions, auricular paroxysmal tachycardia, and paroxysms of auricular fibrillation and auricular flutter (C. G.). In two cases of normal sinus rhythm there were neither premature contractions nor other arrhythmias (E. B. and J. C.), and in one case (P. M.) of auricular fibrillation neither premature contractions nor other changes in rhythm occurred. In three cases (G. S., E. B., and P. M.), the T waves changed moderately in form and amplitude during the operation, and in cases E. B. and P. M. the T waves returned to their preoperative form after closure of the wound. In none of the cases were there significant changes in the R-T segments. The absence of more marked changes in the T waves and R-T segments appeared to indicate that, during resection of the thickened and adherent pericardium, there was only slight damage to the myocardium, even though this involved dissecting the visceral pericardium from the heart muscle. The changes which appeared were transient. The arrhythmias which were recorded were premature contractions, singly and in groups, and short paroxysms of ventricular tachycardia, auricular paroxysmal tachycardia, auricular fibrillation, and auricular flutter. These arrhythmias were of short duration and did not recur in the postoperative period. The signs of congestion that were present before operation showed no marked increase, and circulatory failure did not develop following operation. In the two cases of auricular fibrillation, the paroxysmal rhythms were ventricular in origin. On the other hand, in the one case of normal sinus rhythm, the paroxysmal rhythms were auricular in origin; namely, auricular fibrillation, auricular flutter, and auricular paroxysmal tachycardia.

The changes in the electrocardiograms of these six patients were similar, in part, to those reported by Feil and Rossman[12] in a series of eight cases of chronic constrictive pericarditis. However, the paroxysms of auricular tachycardia, auricular fibrillation, and auricular flutter which occurred in case C. G. did not appear in their series, and the transient ventricular fibrillation, nodal rhythm, and shifting pacemaker which they observed did not occur in our cases. They also recorded changes in the S-T segments in three of their cases which did not occur to any significant degree in our series.

The abnormalities in rhythm which we recorded during resection of the pericardium disappeared promptly with cessation of manipulation, or of traction, or of dissection, of the heart. Judging from observation of the hearts during operation, and because of the brief duration of the irregularities, we did not think it necessary to give quinidine to any of the 13 patients[15] who were subjected to pericardiectomy. As experience increased it did not appear to be indicated as a routine procedure. In one of our 13 cases (not one of the six now being reported), arrhythmia

occurred frequently during one stage of the resection. The use of procaine locally did not appear to decrease the irritability of the muscle. Serial electrocardiograms which were taken for months after operation showed surprisingly few changes in the form of the T waves and R-T segments.

## SUMMARY

1. Electrocardiograms which were taken before, and at intervals during, resection of the pericardium in six cases of chronic constrictive pericarditis have been described.

2. Two patients who had auricular fibrillation developed both right and left ventricular premature contractions and short runs of ventricular paroxysmal tachycardia. In one case of normal sinus rhythm, auricular premature contractions which had been present beforehand increased in frequency. Moreover, paroxysms of auricular fibrillation, auricular flutter, and auricular paroxysmal tachycardia were recorded. Two patients with normal sinus rhythm and one with auricular fibrillation developed neither premature contractions nor other changes in rhythm. In only one case did the electrocardiograms which were taken before and after operation show appreciable changes in the amplitude and form of the T waves.

3. These observations demonstrate the remarkable amount of manipulation and mechanical stimulation of its surface that the heart can tolerate without the occurrence of prolonged abnormalities of rhythm and without embarrassment of its function. These observations should give assurance to surgeons who undertake the surgical treatment of chronic constrictive pericarditis.

## REFERENCES

1. Schmieden and Fischer: Zur Frage der schwieligen Perikarditis, Schweiz. med. Wchnschr. **56**: 489, 1926.
2. Schmieden and Westerman: Operative Management of Chronic Constrictive Pericarditis, Surgery **2**: 350, 1937.
3. Churchill, E. D.: Pericardial Resection in Chronic Constrictive Pericarditis, Ann. Surg. **104**: 516, 1935.
4. Beck, C. S., and Griswold, R. A.: Pericardiectomy in Treatment of Pick's Syndrome, Arch. Surg. **21**: 1064, 1930.
5. Heuer, G. J., and Stewart, H. J.: The Surgical Treatment of Chronic Constrictive Pericarditis, Surg., Gynec., and Obst. **68**: 979, 1939.
6. Stewart, H. J., Heuer, G. J., Deitrick, J. E., Crane, N. F., Watson, R. F., and Wheeler, C. H.: Measurements of the Circulation in Constrictive Pericarditis Before and After Resection of the Pericardium, J. Clin. Investigation **17**: 581, 1938.
7. Stewart, H. J., and Heuer, G. J.: Chronic Constrictive Pericarditis. Dynamics of the Circulation and Results of Surgical Treatment, Arch. Int. Med. **63**: 504, 1939.
8. Blalock, A., and Levy, S.: Tuberculous Pericarditis, J. Thoracic Surg. **7**: 132, 1937.
9. Burwell, C. S., and Flickinger, D.: Obstructing Pericarditis, Arch. Int. Med. **56**: 250, 1935.
10. Burwell, C. S., and Strayhorn, W. D.: Concretio Cordis, Arch. Surg. **24**: 106, 1932.
11. Burwell, C. S., and Blalock, A.: Chronic Constrictive Pericarditis, J. A. M. A. **110**: 265, 1938.

12. Feil, H., and Rossman, P. L.: Electrocardiographic Observations in Cardiac Surgery, Ann. Int. Med. **13**: 402, 1939.
13. Mautz, F. R.: Reduction of Cardiac Irritability by the Epicardial and Systemic Administration of Drugs as a Protection in Cardiac Surgery, J. Thoracic Surg. **5**: 612, 1936.
14. Beck, C. S., and Mautz, F. R.: The Control of the Heart Beat by the Surgeon, Ann. Surg. **106**: 525, 1937.
15. Stewart, H. J., and Heuer, G. J.: Measurements of the Circulation in Chronic Constrictive Pericarditis Before and After Resection of the Pericardium, N. Y. State J. Med. **39**: 2183, 1939.

# THE SPA TREATMENT OF THROMBOANGIITIS OBLITERANS

T. J. Fatherree, M.D., and Cecil Hurst, M.D.
Soap Lake, Wash.

THE town of Soap Lake, Wash., is unique with regard to the number of its citizens who have thromboangiitis obliterans. An unofficial report of the 1940 census credits Soap Lake with a population of 619, and between the months of January and July, 1940, inclusive, thirty-four persons with thromboangiitis obliterans were residing at Soap Lake. Thus, during this period, there was approximately one person with this uncommon disease to every eighteen residents of the town. This high incidence of thromboangiitis obliterans is explained by the fact that the town of Soap Lake is situated on the shores of a mineralized body of water known as Soap Lake, which has acquired a degree of popularity as a spa which influences thromboangiitis obliterans favorably. In recent years many persons with this disease have come to Soap Lake with the hope of obtaining relief by taking baths in the lake, and drinking its mineral water, and some of these people have remained as residents of the town.

In 1939, the State of Washington founded the McKay Memorial Research Hospital for the purpose of studying the problem of thromboangiitis obliterans, with particular reference to the therapeutic effect of the water of Soap Lake and the climate of the Soap Lake vicinity on this disease. In order to throw as much light as possible on this problem, we have made a study, consisting of careful historical records and physical examinations, of the patients with thromboangiitis obliterans who reside at Soap Lake. It was felt that such a study should show whether or not the patients might have received any considerable benefits as a result of this type of therapy and should thus tend to clarify the question which has been raised concerning the effectiveness of the spa treatment of thromboangiitis obliterans at Soap Lake. The results of this study constitute the basis of this report.

Soap Lake, which is approximately 864 acres in area, is situated at the mouth of the Grand Coulee, in the Walla Walla Plateau region of central Washington, a part of the basin of the Columbia River. The elevation is approximately 1,065 feet above sea level. A summary of a chemical analysis of the surface water of Soap Lake, made in March, 1939, by Newhall,[1] Chemical Engineer for the Washington State Board of Health, is given in Table I.

The climate[2] of the Soap Lake region throughout spring, summer, and fall is characterized by much sunshine and scant precipitation. The humidity is comparatively high in the winter, whereas in the warmer

From the McKay Memorial Research Hospital, Soap Lake, Washington.
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TABLE I

| | PARTS PER MILLION | PER CENT SOLIDS |
|---|---|---|
| Sodium | 13,836.95 | 38.04 |
| Carbonate | 7,000.00 | 19.24 |
| Sulphate | 6,572.00 | 18.07 |
| Chloride | 4,437.00 | 12.20 |
| Bicarbonate | 4,280.00 | 11.77 |
| Silica | 74.00 | 0.20 |
| Magnesium | 52.40 | 0.14 |
| Potassium | 36.37 | 0.10 |
| Organic nitrogen | 33.10 | 0.09 |
| Calcium | 7.27 | 0.02 |
| Oil (ichthyol-like) | 29.90 | 0.08 |

Aluminum, iron, copper, rubidium, lithium, and fluoride were detected in minute amounts.

portion of the year it is moderate to low, and, on summer afternoons, it is generally from very low to extremely low. The winter temperatures are at times quite low, whereas the summer temperatures frequently reach very high levels. Generally speaking, from May through September the days are bright, hot, and dry. However, during the late fall, winter, and early spring these conditions do not prevail, and there is likely to be a considerable amount of cold and dampness, with a less abundant supply of sunshine.

The treatment used by the patients included in this study consisted of baths in the water of Soap Lake, drinking the lake water, varying amounts of rest and exposure to the sun, and daily dressings of the ulcerative and gangrenous lesions by the patients themselves. Baths were taken in the lake proper during the hot summer months, and as warm tub baths for periods of twenty to thirty minutes. In addition, foot soaks in the lake water were frequently used for the treatment of ulcerative and gangrenous lesions. It should be emphasized that, aside from the prescribing of narcotics and the performance of amputations by physicians, these patients received practically no medical supervision.

## RESULTS OF STUDY

At the time of this study, which was made during the months of January to July, 1940, inclusive, thirty-four persons with thromboangiitis obliterans were residing at Soap Lake. We obtained the cooperation of thirty-two of these for the purpose of this investigation. All of the patients were men. Data on all patients with vasospastic disturbances, arteriosclerosis obliterans, and other types of peripheral vascular disease, when there was any doubt about the diagnosis, have been excluded from this report to the best of our ability.

Inquiry was made of all patients concerning the diligence with which they took the hydrotherapy under investigation, namely, bathing in, and drinking the water of Soap Lake. Thirty-one (97 per cent) of the patients stated that they had taken baths three to four times weekly, or oftener, either throughout their residence at Soap Lake, or for consider-

able periods of time after the beginning of their residence. At the time of the inquiry only three of the patients (Cases 6, 30, and 31) stated that they no longer bathed in the water of Soap Lake. However, these patients had taken daily baths for twenty-five months, twenty-seven months, and two months, respectively, before discontinuing them. Another exception (Case 8) stated that he had taken one to two baths weekly throughout his residence at Soap Lake.

Fourteen of the subjects (43.8 per cent) stated that they had drunk water from Soap Lake daily during their residence; five (Cases 6, 9, 19, 29, and 31) had drunk it daily for periods of twenty-five months, two weeks, twelve months, eight years, and two months, respectively, before discontinuing it entirely; three (Cases 1, 17, and 30) had drunk it daily for twelve months and afterward one to two times weekly; seven had drunk it regularly three to four times weekly throughout their residence at Soap Lake; one (Case 15) had drunk it three to four times weekly for nine years, and subsequently one to two times weekly; one had drunk it one to two times weekly throughout his residence; and one, just occasionally.

Thus, it is apparent that, on the whole, the patients took the hydrotherapy with a fair degree of consistency and diligence.

The economic status of these thirty-two persons during their residence at Soap Lake was as follows: Eight were self-supporting; five depended upon insurance payments for a part of, or their entire, support; ten were veterans of the World War and received governmental support; eight received aid from the county welfare department and were dependent either partly or entirely upon this aid for their support; and one was supported by his family.

### THE FACTORS OF AGE, RACE, AGE AT ONSET OF SYMPTOMS, DURATION OF SYMPTOMS PRIOR TO BEGINNING RESIDENCE AT SOAP LAKE, PERIOD OF RESIDENCE AT SOAP LAKE, AND THE EXTENT OF SMOKING

The youngest patient was 27 years of age and the oldest, 56; the average age of all the patients was 42.28 years. It is of interest that none of the patients was Jewish. The youngest age at onset of symptoms was 19 years, the oldest, 49, and the average, 29.41 years. The shortest period of duration of symptoms prior to the beginning of the patient's residence at Soap Lake was one year, the longest, twenty-two years, and the average, ten years. The time of residence at Soap Lake varied from seven months to ten years, and the average was 2.67 years. Some of the patients were away from Soap Lake during their period of residence for varying lengths of time, as follows: Case 1, seven months; Case 10, two months; Case 18, four months; Case 25, one month; Case 26, four months; Case 27, twenty-eight months; Case 29, forty months; Case 31, twenty months; and Case 32, six months.

Smokers were classified as follows: Grade I, five cigarettes, or less, daily; Grade II, five to fifteen cigarettes daily; Grade III, fifteen to twenty-five cigarettes daily; Grade IV, more than twenty-five cigarettes daily. All of the patients were smokers at one time or another. Before beginning their residence at Soap Lake, two (6.3 per cent) were Grade I smokers, nine (28.1 per cent) were Grade II smokers, eighteen (56.2 per cent) were Grade III smokers, and three (9.4 per cent) were Grade IV smokers. One (Case 10) quit smoking six years, and another (Case 24) eighteen months, prior to beginning residence at Soap Lake. Neither of these patients resumed smoking. During their Soap Lake residence, four patients, 12.5 per cent) were Grade I smokers, seven (21.9 per cent), Grade II, sixteen (50 per cent), Grade III, and one (3.1 per cent), Grade IV, while four of the patients (Cases 2, 10, 18, and 24) did not smoke at all.

### THE FACTOR OF OCCUPATION

Originally, twenty-two (69 per cent) of these patients were engaged in occupations requiring manual labor, and ten (31 per cent were engaged in sedentary occupations. Twelve patients (37 per cent) were employed at their usual occupations until the time of their arrival at Soap Lake; seven (22 per cent) had modified their occupations on an average of 3.2 years before coming to Soap Lake; and thirteen (41 per cent) had given up their occupations completely on an average of 3.9 years before coming to Soap Lake. On the other hand, during their residence at Soap Lake only five patients (16 per cent) were engaged in their usual occupation, nine (28 per cent) in a modified type of occupation, and eighteen (56 per cent) did no work at all. In all instances a modification of occupation resulted in work requiring less physical activity.

### THE OCCURRENCE OF SUPERFICIAL THROMBOPHLEBITIS BEFORE AND DURING SOAP LAKE RESIDENCE

Twenty-one patients (66 per cent) had recurrent attacks of superficial phlebitis prior to their residence at Soap Lake, and twenty (62.5 per cent) had recurrent attacks during their Soap Lake residence. Of the twenty-one patients who had phlebitis prior to living at Soap Lake, sixteen (76 per cent) continued to have recurrent attacks during their residence at Soap Lake. Of the sixteen patients who continued to have recurrent attacks of phlebitis while residing at Soap Lake, nine had phlebitis at the same rate of frequency, one had it more often, and six, less frequently. Of the eleven patients who had no phlebitis prior to residence, four developed phlebitis after coming to Soap Lake. Seven of the patients who had no phlebitis prior to coming to Soap Lake did not develop it while residing there. Of the twenty patients who had phlebitis while residing at Soap Lake, ten (50 per cent) had recurrent attacks over a period constituting 90 to 100 per cent of the time spent

TABLE II

PATIENTS WITH THROMBOANGIITIS OBLITERANS RESIDING AT SOAP LAKE, WASHINGTON

| CASE NO. | AGE (YEARS) | RACE | AGE AT ONSET (YEARS) | DURATION PRIOR TO SOAP LAKE RESIDENCE (YEARS) | TIME OF RESIDENCE AT SOAP LAKE (MONTHS) | SMOKING | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | BEFORE SOAP LAKE RESIDENCE | | | | DURING SOAP LAKE RESIDENCE | | | |
| | | | | | | I | II | III | IV | I | II | III | IV |
| 1 | 36 | German-English | 29 | 5 | 26 | | | x | | | | x | |
| 2 | 45 | French | 32 | 12 | 12 | | | | x | | | | |
| 3 | 43 | German-French-Irish | 29 | 11 | 37 | | | x | | | | x | |
| 4 | 56 | French-American | 49 | 4 | 32 | | x | | | | x | | |
| 5 | 50 | German-Irish | 30 | 17 | 37 | | x | | | x | | | |
| 6 | 44 | Scotch | 19 | 22 | 37 | | | x | | | | x | |
| 7 | 48 | English | 27 | 18 | 33 | | | x | | | | x | |
| 8 | 42 | English | 27 | 14 | 8 | | | x | | | | x | |
| 9 | 40 | German-English | 28 | 11 | 10 | | | x | | x | | | |
| 10 | 40 | Irish | 33 | 6 | 12 | | | x | | | | | |
| 11 | 43 | American | 29 | 11 | 33 | | x | | | | x | | |
| 12 | 27 | Scotch-Irish | 19 | 5 | 39 | | | x | | | | x | |
| 13 | 47 | Scotch-Irish | 44 | 1 | 32 | | | | x | | | | x |
| 14 | 36 | English | 30 | 3 | 35 | | x | | | | x | | |
| 15 | 51 | English-Irish | 31 | 10 | 120 | | | x | | | | x | |
| 16 | 43 | Scotch-Irish | 31 | 11 | 16 | | | x | | | | x | |
| 17 | 48 | Irish | 26 | 18 | 52 | | | x | | | | x | |
| 18 | 43 | Scotch | 41 | 1 | 16 | | | | x | | | | |
| 19 | 34 | American | 24 | 1 | 35 | | | x | | | | x | |
| 20 | 34 | German-Scotch | 26 | 6 | 21 | | | x | | | | x | |
| 21 | 45 | Scotch-Irish | 29 | 14 | 21 | | | x | | | | x | |
| 22 | 47 | German-Irish | 39 | 7 | 12 | | | x | | | | x | |
| 23 | 41 | French-English | 31 | 8 | 30 | x | | | | x | | | |
| 24 | 34 | American | 26 | 7 | 8 | | | x | | | | | |
| 25 | 47 | German-French | 27 | 19 | 13 | | | x | | | | x | |
| 26 | 46 | Irish | 23 | 21 | 26 | | x | | | | x | | |
| 27 | 40 | German-English | 27 | 9 | 48 | | x | | | | x | | |
| 28 | 37 | American | 29 | 7 | 7 | | | x | | | | x | |
| 29 | 47 | American | 25 | 12 | 117 | | x | | | | x | | |
| 30 | 45 | American | 31 | 11 | 36 | | x | | | | x | | |
| 31 | 46 | American | 26 | 17 | 36 | | x | | | | | x | |
| 32 | 28 | Norwegian | 24 | 1 | 31 | x | | | | x | | | |

Any one case number refers to the same patient in all tables.

TABLE III

THE OCCURRENCE OF PHLEBITIS IN PATIENTS WITH THROMBOANGIITIS OBLITERANS BEFORE AND DURING RESIDENCE AT SOAP LAKE

| CASE NO. | PRIOR TO SOAP LAKE RESIDENCE | | | DURING SOAP LAKE RESIDENCE | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | RECURRENT ATTACKS OF PHLEBITIS | | PERIOD OF TIME DURING WHICH ATTACKS OCCURRED (YEARS) | RECURRENT ATTACKS OF PHLEBITIS | | TIME OF RESIDENCE AT SOAP LAKE PRIOR TO MOST RECENT ATTACK (MONTHS) | FREQUENCY OF ATTACKS AS COMPARED WITH FREQUENCY PRIOR TO SOAP LAKE RESIDENCE | | |
| | PRESENT | ABSENT | | PRESENT | ABSENT | | LESS | MORE | SAME |
| 1 | | x | | | x | | | | |
| 2 | x | | 11 | | x | | | | |
| 3 | x | | 2 | x | | 35 | | | x |
| 4 | | x | | x | | 32 | | | |
| 5 | x | | 8 | x | | 25 | x | | |
| 6 | x | | 6 | x | | 31 | | x | |
| 7 | x | | NS | x | | 33 | x | | |
| 8 | | x | | x | | 8 | | | |
| 9 | x | | NS | | x | | | | |
| 10 | | x | | | x | | | | |
| 11 | x | | 4 | x | | 15 | | | x |
| 12 | x | | 4½ | x | | 27 | | | x |
| 13 | | x | | x | | 26 | | | |
| 14 | | x | | | x | | | | |
| 15 | x | | 1 | x | | 114 | | | x |
| 16 | x | | 11 | x | | 12 | | | x |
| 17 | x | | 18 | x | | 51 | x | | |
| 18 | | x | | | x | | | | |
| 19 | x | | NS | | x | | | | |
| 20 | x | | 6 | x | | 16 | | | x |
| 21 | x | | NS | x | | 15 | | | x |
| 22 | x | | 7 | x | | 11 | | | x |
| 23 | x | | 9 | x | | 30 | x | | |
| 24 | x | | 7 | | x | | | | |
| 25 | | x | | | x | | | | |
| 26 | x | | 1 | x | | 15 | x | | |
| 27 | | x | | | x | | | | |
| 28 | x | | 7 | x | | 7 | | | x |
| 29 | x | | NS | | x | | | | |
| 30 | x | | 2 | x | | 34 | x | | |
| 31 | | x | | x | | 24 | | | |
| 32 | | x | | | x | | | | |

NS, Not stated in record of case.

at Soap Lake, two (10 per cent), 80 to 89 per cent, three, 70 to 79 per cent, three, 60 to 69 per cent, one, 50 to 59 per cent, and one over a period constituting 40 to 49 per cent of the time spent at Soap Lake, all dating from the beginning of residence. Thus, fifteen (75 per cent) of the patients had phlebitis for periods greater than 69 per cent, whereas only five (25 per cent) had phlebitis for periods less than 69 per cent of the time spent at Soap Lake, dating from the beginning of their residence.

### THE OCCURRENCE OF ULCERATION AND GANGRENE AND THE INCIDENCE AND TIME OF HEALING OF THESE LESIONS BEFORE AND DURING SOAP LAKE RESIDENCE

For the purpose of simplification, ulceration and gangrene are spoken of here as occurring in attacks. An attack of ulceration with or without gangrene was defined arbitrarily as a lesion consisting of either ulceration, gangrene, or both, on one extremity, or one or more lesions at the same time on the same extremity. Thus, if one toe became gangrenous or ulcerated and subsequently another area of the same foot became ulcerated or gangrenous before the initial lesion had healed or had led to amputation, the entire process to the point of healing or amputation was considered as a single attack. However, if two extremities were involved at one time, the lesions were considered as constituting two attacks. Postoperative ulceration or gangrene which failed to heal after a major amputation, so that reamputation was necessary, or persisted for a period of more than three months, was considered as constituting an attack different from the lesion for which the amputation was performed. However, failure of the lesion to heal after a minor amputation was not considered an attack different from that for which the amputation was performed. Twenty-nine patients (91 per cent) had a total of 125 attacks of gangrene with or without ulceration prior to coming to Soap Lake, whereas seventeen patients (53 per cent) developed a total of thirty-seven attacks of gangrene with or without ulceration during their Soap Lake residence. Inasmuch as the average duration of the disease prior to Soap Lake residence was ten years, and the average time of residence of these patients at Soap Lake was 2.67 years, the patients obviously had more time to develop ulceration and gangrene before their arrival at Soap Lake than during their stay there. Hence, the development of ulceration and gangrene was computed on the basis of the average number of attacks per patient per average number of years of duration of symptoms for the periods before and during Soap Lake residence. This computation was made, first, by dividing the total number of attacks of gangrene with or without ulceration in a given period by the total number of patients in the series, for the purpose of obtaining the average number of attacks of ulceration with or without gangrene per patient. This figure was then divided by the figure repre-

senting the average duration, in years, of the period being investigated. The result represents the average number of attacks of ulceration with or without gangrene per patient per average number of years of duration of the period being investigated. When computed on this basis, it was found that the average number of attacks per patient per average number of years of duration of the disease prior to Soap Lake residence was 0.39, whereas the figure calculated on the same basis for the duration of residence at Soap Lake was 0.43.

Of the twenty-nine patients who had 125 attacks of ulceration with or without gangrene prior to the beginning of Soap Lake residence, fifteen recovered from thirty-six attacks (29 per cent) prior to coming to Soap Lake, whereas eighty-nine attacks (71 per cent) which developed in twenty-five cases prior to residence at Soap Lake failed to heal, and either led to amputation or were still present when the patients came to Soap Lake. Of the fifteen patients with one or more attacks of ulceration with or without gangrene from which they recovered, we obtained data on fourteen concerning how long it took to recover; the average time was 4.3 months.

Of the seventeen patients who had a total of thirty-seven attacks of ulceration with or without gangrene while residing at Soap Lake, thirteen recovered from twenty-four attacks (65 per cent) in an average time of 5.8 months, whereas thirteen attacks (35 per cent) in nine cases continued and either led to amputation or were still present when the patients were interviewed by us.

The time of appearance of the thirty-seven attacks of ulceration after beginning residence at Soap Lake was as follows: Eight developed within the first six months; eight, within seven to twelve months; nine, within the second year; seven, within the third year; three, within the fourth year; and two, within the ninth year.

Of the twenty-five patients who developed ulceration with or without gangrene which failed to heal prior to coming to Soap Lake, eighteen had a total of twenty-five attacks on arrival. Fourteen patients recovered from seventeen attacks (68 per cent) in an average time of 8.4 months, and five patients did not recover from eight attacks (32 per cent).

### THE INCIDENCE OF AMPUTATION BEFORE AND DURING SOAP LAKE RESIDENCE

The total number of patients who had had amputations, either major, minor, or both, prior to beginning residence at Soap Lake was sixteen (50 per cent). During this period there were twenty-seven major amputations in fifteen cases (47 per cent), and forty-five minor amputations in eight cases (25 per cent), making a total of seventy-two amputations in sixteen cases. The average number of major amputations per patient was 0.843, whereas the average number of major amputations per patient per average number of years of duration of the disease prior to

TABLE IV

THE OCCURRENCE AND PROGRESS OF ULCERATION AND GANGRENE PRIOR TO AND DURING RESIDENCE AT SOAP LAKE

| CASE NO. | PRIOR TO SOAP LAKE RESIDENCE | | | | ON ARRIVAL AT SOAP LAKE | | | | DURING SOAP LAKE RESIDENCE | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | ATTACKS OF GANGRENE AND/OR ULCERATION | | | | GANGRENE AND/OR ULCERATION PRESENT | | | | DEVELOPMENT OF GANGRENE AND/OR ULCERATION | | | |
| | TOTAL NO. | HEALED | AV. TIME OF HEALING (MONTHS) | FAILED TO HEAL | NO. OF EPISODES | HEALED | TIME OF HEALING (MONTHS) | FAILED TO HEAL | NO. OF EPISODES | HEALED | AV. TIME OF HEALING (MONTHS) | FAILED TO HEAL |
| 1 | 2 | 0 | | 2 | 0 | 0 | | 0 | 2 | 0 | | 2 |
| 2 | 7 | 6 | 4 | 1 | 1 | 1 | 1½ | 0 | 0 | 0 | | 0 |
| 3 | 1 | 0 | | 1 | 0 | 0 | | 0 | 0 | 0 | | 0 |
| 4 | 3 | 0 | | 3 | 0 | 0 | | 0 | 0 | 0 | | 0 |
| 5 | 8 | 4 | NS | 4 | 0 | 0 | | 0 | 3 | 1 | 27 | 2 |
| 6 | 4 | 4 | 5 | 0 | 0 | 0 | | 0 | 6 | 3 | 1 | 3 |
| 7 | 4 | 0 | | 4 | 3 | 0 | | 3 | 0 | 0 | | 0 |
| 8 | 5 | 0 | | 5 | 0 | 0 | | 0 | 0 | 0 | | 0 |
| 9 | 0 | 0 | | 0 | 0 | 0 | | 0 | 0 | 0 | | 0 |
| 10 | 4 | 2 | 3 | 2 | 2 | 2 | 7 | 0 | 0 | 0 | | 0 |
| 11 | 4 | 1 | 6 | 3 | 2 | 0 | | 2 | 0 | 0 | | 0 |
| 12 | 1 | 0 | | 1 | 1 | 1 | 12 | 0 | 3 | 2 | 7½ | 1 |
| 13 | 1 | 0 | | 1 | 1 | 1 | 1 | 0 | 3 | 2 | 2 | 1 |
| 14 | 1 | 0 | | 1 | 1 | 1 | 22 | 0 | 0 | 0 | | 0 |
| 15 | 4 | 1 | 6 | 3 | 1 | 1 | 12 | 0 | 2 | 2 | 5 | 0 |
| 16 | 3 | 0 | | 3 | 1 | 1 | ½ | 0 | 2 | 2 | 2½ | 0 |
| 17 | 1 | 1 | 1 | 0 | 0 | 0 | | 0 | 3 | 2 | 6 | 1 |
| 18 | 1 | 1 | 1 | 0 | 0 | 0 | | 0 | 0 | 0 | | 0 |
| 19 | 0 | 0 | | 0 | 0 | 0 | | 0 | 2 | 2 | 2 | 0 |
| 20 | 0 | 0 | | 0 | 0 | 0 | | 0 | 1 | 1 | 9 | 0 |
| 21 | 2 | 0 | | 2 | 0 | 0 | | 0 | 0 | 0 | | 0 |
| 22 | 3 | 0 | | 3 | 1 | 0 | | 1 | 1 | 0 | | 1 |
| 23 | 3 | 2 | 3 | 1 | 1 | 1 | 3 | 0 | 1 | 1 | 3 | 0 |
| 24 | 6 | 5 | 2 | 1 | 1 | 1 | 1 | 0 | 3 | 3 | 1½ | 0 |
| 25 | 5 | 2 | 18 | 3 | 1 | 0 | | 1 | 0 | 0 | | 0 |
| 26 | 2 | 1 | 3 | 1 | 1 | 1 | 1½ | 0 | 1 | 1 | 3 | 0 |
| 27 | 4 | 1 | 2 | 3 | 1 | 1 | 2 | 0 | 0 | 0 | | 0 |
| 28 | 2 | 0 | | 2 | 0 | 0 | | 0 | 0 | 0 | | 0 |
| 29 | 35 | 0 | | 35 | 4 | 3 | 12 | 1 | 1 | 0 | | 1 |
| 30 | 7 | 4 | 6 | 3 | 1 | 1 | 36 | 0 | 1 | 0 | | 1 |
| 31 | 1 | 0 | | 1 | 1 | 1 | 6 | 0 | 2 | 2 | 6 | 0 |
| 32 | 1 | 1 | 1 | 0 | 0 | 0 | | 0 | 0 | 0 | | 0 |

NS, Not stated in record.

TABLE V

THE INCIDENCE OF AMPUTATION PRIOR TO AND DURING SOAP LAKE RESIDENCE

| CASE NO. | PRIOR TO SOAP LAKE RESIDENCE | | DURING SOAP LAKE RESIDENCE | | | | | | | | | | | | PRIOR TO AND DURING SOAP LAKE RESIDENCE |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | AMPUTATIONS | | AMPUTATIONS | | TIME AT SOAP LAKE PRIOR TO AMPUTATIONS | | | | | | | | | | TOTAL NO. OF MAJOR AMPUTATIONS |
| | | | | | 0-6 MO. | | 7-12 MO. | | 2ND YR. | | 3RD YR. | | 4TH YR. | | |
| | MAJOR | MINOR | MAJOR | MINOR | MAJOR | MINOR | MAJOR | MINOR | MAJOR | MINOR | MAJOR | MINOR | MAJOR | MINOR | |
| 1 | 2 | 0 | 2 | 0 | | | | | 2 | | | | | | 4 |
| 2 | 0 | 0 | 0 | 0 | | | | | | | | | | | 0 |
| 3 | 1 | 0 | 0 | 0 | | | | | | | | | | | 1 |
| 4 | 3 | 0 | 0 | 0 | | | | | | | | | | | 3 |
| 5 | 2 | 1 | 0 | 0 | | | | | | | | | | | 2 |
| 6 | 0 | 0 | 3 | 0 | | | 1 | | | | 2 | | | | 3 |
| 7 | 1 | 8 | 0 | 0 | | | | | | | | | | | 1 |
| 8 | 3 | 2 | 0 | 0 | | | | | | | | | | | 3 |
| 9 | 0 | 0 | 0 | 0 | | | | | | | | | | | 0 |
| 10 | 0 | 0 | 0 | 0 | | | | | | | | | | | 0 |
| 11 | 1 | 0 | 0 | 0 | | | | | | | | | | | 1 |
| 12 | 0 | 0 | 1 | 0 | | | | | 1 | | | | | | 1 |
| 13 | 0 | 0 | 0 | 3 | | | | 3 | | | | | | | 0 |
| 14 | 0 | 0 | 0 | 0 | | | | | | | | | | | 0 |
| 15 | 2 | 0 | 0 | 0 | | | | | | | | | | | 2 |
| 16 | 1 | 1 | 0 | 0 | | | | | | | | | | | 1 |
| 17 | 0 | 0 | 1 | 0 | | | | | | | 1 | | | | 1 |
| 18 | 0 | 0 | 0 | 0 | | | | | | | | | | | 0 |
| 19 | 0 | 0 | 0 | 0 | | | | | | | | | | | 0 |
| 20 | 0 | 0 | 0 | 0 | | | | | | | | | | | 0 |
| 21 | 2 | 0 | 0 | 0 | | | | | | | | | | | 2 |
| 22 | 1 | 1 | 2 | 0 | 2 | | | | | | | | | | 3 |
| 23 | 0 | 0 | 0 | 0 | | | | | | | | | | | 0 |
| 24 | 0 | 0 | 0 | 0 | | | | | | | | | | | 0 |
| 25 | 1 | 1 | 1 | 0 | | | 1 | | | | | | | | 2 |
| 26 | 0 | 0 | 1 | 0 | | | | | | | 1 | | | | 1 |
| 27 | 2 | 0 | 0 | 0 | | | | | | | | | | | 2 |
| 28 | 2 | 0 | 0 | 0 | | | | | | | | | | | 2 |
| 29 | 3 | 28 | 1 | 1 | | 1 | | | | | | | 1 | | 4 |
| 30 | 0 | 3 | 0 | 0 | | | | | | | | | | | 0 |
| 31 | 0 | 0 | 0 | 0 | | | | | | | | | | | 0 |
| 32 | 0 | 0 | 0 | 0 | | | | | | | | | | | 0 |

the beginning of Soap Lake residence was 0.08. In comparison to this, during their residence at Soap Lake ten patients (31 per cent) had a total of sixteen amputations. Eight patients (25 per cent) had a total of twelve major amputations, and two (6 per cent) had a total of four minor amputations. The average number of major amputations per patient during Soap Lake residence was 0.38, whereas the average number of major amputations per patient per average number of years of residence was 0.14.

The intervals between beginning residence at Soap Lake and major amputations were as follows: One patient had two major amputations during the first six months; two had amputations within seven to twelve months; two had three amputations in the second year; three had four amputations in the third year; and one had an amputation in the fourth year of residence. The minor amputations were distributed as follows: One in the first six months and three within seven to twelve months.

Of the entire group of thirty-two patients, nineteen (59 per cent) had had major amputations at the time this survey was made.

### THE PROGRESS OF INTERMITTENT CLAUDICATION AT SOAP LAKE

Twenty-three (72 per cent) of the thirty-two patients stated that they had had intermittent claudication on arrival at Soap Lake. During their residence, seven (30.4 per cent) improved, eleven (47.8 per cent) remained the same, five (21.7 per cent) became worse, and one patient, who did not have claudication prior to residence, developed it.

### THE OCCURRENCE OF ARTERIAL OCCLUSION IN PATIENTS RESIDING AT SOAP LAKE

During the period from July, 1939, to July, 1940, we observed four patients who had an extension of their arterial occlusion between the time of the initial and subsequent examination. In August, 1939, one patient (Case 1) had normal pulsations in the popliteal and dorsalis pedis arteries on the left. In September, 1939, he developed an acute arterial occlusion, with absence of pulsation in the left popliteal and dorsalis pedis arteries. Massive gangrene of the left foot developed, necessitating amputation two weeks later. This patient had resided at Soap Lake seventeen months at the time of the acute arterial occlusion. Another patient (Case 4) was first examined March 23, 1940, at which time the pulsation in the right radial artery was normal. The pulsation in the left ulnar artery was graded II (IV representing a normal pulsation, and 0, no pulsation). The popliteal artery on the left was graded II. The patient was subsequently examined May 25, 1940, after he had resided thirty-one months at Soap Lake. At this time the right radial, the left ulnar, and the left popliteal arteries did not pulsate. The history given at this time was of an acute arterial occlusion approximately one week previously, involving the left lower extremity.

Subsequently, he developed severe rest pain and gangrene of the left great toe. Another patient (Case 22) was first examined April 12, 1940, at which time the radial artery on the right did not pulsate, but the ulnar artery on the right pulsated normally. Subsequent examination, May 14, 1940, after he had resided for twenty-eight months at Soap Lake, showed absence of pulsation in the right ulnar artery. The patient subsequently developed ulceration of the right index finger. The fourth patient (Case 23) was first examined in October, 1939, at which time the left radial artery pulsated normally. When examined Dec. 13, 1939, after he had resided for five months at Soap Lake, the left radial artery did not pulsate. Subsequently the patient developed an ulcer of the left index finger.

### THE OPINION OF THE PATIENTS AS TO THEIR PROGRESS AT SOAP LAKE

Twenty-five of the patients stated that they had obtained substantial symptomatic relief; five, that they had noticed no symptomatic improvement; and two, that they were undecided with regard to the question of symptomatic improvement.

### COMMENT

We have presented the results of a study of thirty-two patients with thromboangiitis obliterans residing at Soap Lake for the purpose of attempting to evaluate the effectiveness of the spa treatment of this disease at Soap Lake. The opportunity for this type of study was excellent because the patients had subjected themselves to the treatment over relatively long periods of time, and had not used any other kind of treatment, and because we had opportunity to interview and examine them.

A consideration of the smoking factor, as it applied to the patients before and while residing at Soap Lake, shows that a large percentage of the patients smoked both before and after coming to Soap Lake, and, therefore, this factor could hardly be considered of importance in so far as it might have affected the comparative progress of the disease before and during residence at Soap Lake.

When the group was considered from the occupational standpoint, the conditions were somewhat more favorable during their residence at Soap Lake than they were prior to arrival, for more of them were doing no work at all, and fewer of them were engaged in their usual occupations.

Perhaps the most convincing evidence against the specificity of the treatment available at Soap Lake for thromboangiitis obliterans is the data regarding the occurrence of recurrent phlebitis before and during residence at Soap Lake, and the fact that four patients had a progression of their arterial occlusion after considerable periods of residence at Soap Lake. The fact that 63 per cent of these patients continued to have phlebitis after coming to Soap Lake and that 75 per cent of the

patients who did have phlebitis had it over periods of 70 per cent or more of the time which they spent at Soap Lake indicates that the treatment available at Soap Lake does not arrest the activity of the disease.

A consideration of the ulcerative and gangrenous lesions of these patients before and after coming to Soap Lake is of interest. A computation of the rate of development of ulcerative or gangrenous lesions per patient per average number of years of duration of the disease for the periods representing the duration of the symptoms before and during Soap Lake residence indicates that the patients developed these lesions at a slightly greater rate after they came to Soap Lake. It is well appreciated that these figures imply trends, rather than mathematical exactness, because there are many factors which might influence them. However, they are of value in showing that the treatment of thromboangiitis obliterans at Soap Lake, under the conditions which have been described, does not influence appreciably the development of ulceration and gangrene.

It is of interest that, of the ulcerative and gangrenous lesions which developed in these cases before the patients came to Soap Lake, 71 per cent failed to heal prior to the beginning of residence. In contrast to this, of the twenty-five separate instances of ulceration or gangrene which were present in eighteen patients upon their arrival at Soap Lake, seventeen (68 per cent) in fourteen patients healed in an average time of 8.4 months after arrival, and eight (32 per cent) in five patients failed to heal. The lesions of three of the patients which failed to heal led to one minor and two major amputations, and the lesions of the remaining two patients were still present at the time of this survey. Furthermore, of the thirty-seven attacks of ulceration with or without gangrene which developed in seventeen patients during their residence at Soap Lake, twenty-four attacks in thirteen patients (65 per cent) healed in an average time of 3.8 months, and thirteen attacks (35 per cent) in nine patients failed to heal. The lesions of seven of the patients which failed to heal led to nine major and three minor amputations, while the lesions of two of the patients were still present at the time of the survey.

Thus, there were sixty-two attacks of ulceration with or without gangrene in twenty-four patients who were subjected to the form of treatment under consideration. Of these, forty-one (66 per cent) healed and twenty-one (34 per cent) failed to heal.

Twenty-five per cent of the patients included in this study had major amputations during their residence at Soap Lake. A computation of the number of major amputations per patient per average year of residence shows that the rate of major amputation was somewhat higher in these patients during residence than was the case prior to their residence at Soap Lake.

For comparison, it may be noted that McKittrick[3] reported that 31 per cent of the patients with thromboangiitis obliterans who were admitted to the Massachusetts General Hospital from 1929 to 1939 had major amputations before leaving the hospital, and Horton[4] stated that 15.6 per cent of the patients with thromboangiitis obliterans who were treated at the Mayo Clinic from 1907 to 1937, inclusive, had amputations at the clinic. In this connection, Silbert[5] has stated that, before the institution of modern types of therapy, 60 per cent of the patients with ulceration or gangrene had amputations. However, Samuels[6] reported treating more than 300 patients with thromboangiitis obliterans without having to do more than one major amputation, and Silbert reported an amputation incidence of only 6.4 per cent in a series of 687 cases in which the patients were treated with hypertonic saline intravenously.

The explanation for the popularity of Soap Lake as a spa for the treatment of thromboangiitis obliterans undoubtedly lies in the considerable percentage (66 per cent in the cases included in this study) of gangrenous and ulcerative lesions which heal while the patients are treating themselves at Soap Lake.

It is remarkable that these patients, who were practically without medical supervision, and who, for the most part, smoked excessively, progressed as favorably as they did. To what extent, if any, the spa treatment has influenced the progress of the disease is difficult to say. However, in our opinion, the frequent healing of gangrenous and ulcerative lesions at Soap Lake emphasizes the ever-present tendency that these lesions have toward healing, provided they are kept at rest, kept clean, and not subjected to meddlesome surgical procedures.

Any attempt to evaluate the beneficial effects of taking baths and foot soaks in the water of Soap Lake on the gangrenous and ulcerative lesions of thromboangiitis obliterans is hampered greatly by the fact that, practically, it is impossible to treat the lesions with this measure alone. The very nature of the lesions demands a certain amount of rest. The tendency on the part of the patient, however, is to give the major share of the credit for the healing of a lesion to the particular type of treatment which was being used when healing occurred. This tendency is not peculiar to patients, for it may be observed frequently in medical reports concerning the treatment of thromboangiitis obliterans and other chronic diseases. For instance, if patients with gangrenous and ulcerative lesions are treated with rest in bed, heat, foot soaks, and typhoid vaccine intravenously, to give a specific example, the tendency on the part of the observer, frequently, is to give the major share of the credit for any healing which occurs to the more spectacular part of the treatment, which in this instance happens to be typhoid vaccine. Specious reasoning of this type impedes rather than hastens the reasonable evaluation of therapy. The observations reported here serve, it seems to us, to emphasize the well-known but often disregarded fact

that the majority of the gangrenous and ulcerative lesions of thromboangiitis obliterans, if kept at rest, kept clean, and spared the trauma incident to ill-advised local surgical procedures, will heal of their own accord.

## CONCLUSIONS

1. This study indicates that the spa treatment of thromboangiitis obliterans at Soap Lake, Washington, is not a specific treatment for this disease.

2. The ulcerative and gangrenous lesions of the patients who were studied healed in a large percentage of cases.

## REFERENCES

1. Newhall, C. A.: Personal communication to the authors.
2. U. S. Dept. of Agriculture Weather Bureau: Climactic Summary of the United States. Section 2. Eastern Washington.
3. McKittrick, L. S.: The Diagnosis and Management of Chronic Obliterative Vascular Disease, J. A. M. A. **113:** 1223, 1939.
4. Horton, B. T.: The Outlook in Thrombo-Angiitis Obliterans, J. A. M. A. **111:** 2184, 1938.
5. Silbert, S.: Clinical Evidence Upon Which the Use of Tobacco May Be Incriminated as the Essential Cause of Thrombo-Angiitis Obliterans, S. Clin. North America **18:** 389, 1938.
6. Samuels, S. S.: Gangrene Due to Thrombo-Angiitis Obliterans, J. A. M. A. **102:** 436, 1934.

# THE SIGNIFICANCE OF LOW VOLTAGE OF THE QRS COMPLEX IN PRECORDIAL LEADS

## Comparison With Low Voltage in Limb Leads

Samuel Bellet, M.D., and Alfred Kershbaum, M.D.
Philadelphia, Pa.

THE significance of low voltage of the QRS complexes in the limb leads of the electrocardiogram has been discussed by many observers.[1] There can be little question that, in many instances, low voltage complexes are a result of severe myocardial disease. However, this is by no means always so, for complexes which are definitely below the accepted limits of normal are often observed when there is only slight myocardial involvement, and even when the heart is normal. Although Willius and Killins[2] attributed to myocardial disease the low voltage which they found in 32 per cent of 140 cases, they feel that low voltage which is unassociated with other graphic abnormalities neither indicates serious myocardial disease necessarily, nor, ipso facto, is of serious prognostic import. The diagnosis of myocardial disease, although it may be suggested, cannot be made positively upon the evidence of low voltage alone.

As far as we are aware, the literature contains no study of the significance of low voltage of the QRS complexes in precordial leads. The lack of correspondence between the amplitude of different precordial leads and that of the limb leads is well recognized.[3, 4, 5] Usually, low voltage in the limb leads, even when it results from severe myocardial disease, is accompanied by normal voltage in the precordial leads. Much less frequently have we observed that low voltage was present in both limb and precordial leads. The present study is an attempt to evaluate the factors which are responsible for this agreement, and the significance of curves in which the voltage of the QRS complexes is low in both limb and chest leads.

### METHOD

For this study, twenty cases of low voltage in both limb and precordial leads, in which our studies were complete, were collected. The observations in this group were compared with those in fifty consecutive cases in which there was low voltage in the limb leads and normal voltage in the precordial leads. In addition, 300 normal subjects were examined for the possible presence of low voltage in the limb and precordial leads. Since pericardial disease, both with effusion and of the adherent type, is sometimes associated with low voltage, the electrocardiograms of seventy-seven patients with this disease were also reviewed.

From The Division of Cardiology of the Philadelphia General Hospital and the Robinette Foundation, University of Pennsylvania.
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The voltage was regarded as low when the greatest deflection of the QRS complex did not exceed 5 to 6 mm. in either direction from the isoelectric line. This is in accord with the criteria of Sprague and White,[6] although Pardee[7] sets the lower limit of normal as 7 mm.*

Just as one does not rely upon a single lead to establish low voltage in the limb leads, one should not rely upon a single precordial lead. All of the electrocardiograms included in our series were taken by the old method[8] of applying the precordial electrodes, i.e., old Lead IV, V, VI† were used (Figs. 1 to 6). Therefore, in all of the cases both an anteroposterior chest lead (CB lead) and an apex to left leg lead (CF lead) were taken. The voltage was regarded as low when the amplitude of the QRS complex in all of the precordial leads did not exceed 5 to 6 mm. in either direction from the isoelectric line. How important it is to use CB and CF leads is illustrated by Fig. 2. Lead IV (or IVB reversed) is of considerable amplitude; Lead V (IVF reversed) has a voltage of only 5 mm. The above emphasizes the fact that the voltage in the precordial leads should not be regarded as low unless anteroposterior (CB leads), as well as apex to left leg (CF leads), have been taken.‡ In Figs. 3 to 6, although different precordial leads were taken, only one precordial lead (CB), that displaying the greatest amplitude, is shown.

All tracings were carefully standardized so that the string yielded a deviation of 1 cm. for each millivolt of current. Patients were either in the recumbent or sitting position while the electrocardiograms were being taken. In serial tracings on any one patient, the same position was always assumed.

## OBSERVATIONS

The data on the twenty cases in which there was low voltage in both the precordial and limb leads are summarized in Table I, and show two rather striking things. The first was the fact that severe myocardial damage was present in all of the twenty cases (100 per cent), as shown by clinical examination, the electrocardiogram, and, in three instances, by necropsy studies. Eleven of the patients (55 per cent) died during the period of observation in the hospital. The second noteworthy point was the large number of instances of myocardial infarction (eleven cases, 55 per cent). Of these, infarction involving the anterior and posterior portions of the heart was present in five cases§ (25 per cent), and anterior infarction alone in six cases. The possible significance of these facts will be discussed subsequently. In the remaining cases the etiology was as follows: arteriosclerotic, five; rheumatic, two; syphilitic, one; and tuberculous pericarditis, one. Clinically manifest edema of various degrees was present in nine (45 per cent) of these cases.

In this series, seventeen patients had electrocardiographic changes which were characteristic of myocardial disease, in addition to the low

*Low voltage in the limb leads may occasionally be produced as an artifact by some fault in the electrocardiographic apparatus. We have also occasionally observed its appearance in precordial leads as a result of faulty application of the precordial electrode. We believe that neither of these factors applies in any of our cases. In most of these cases, the low voltage was observed in repeated electrocardiographic tracings over a considerable period of time.

†Lead IV is IVB reversed.[9] Lead V is IVF reversed. In Lead VI, the left arm electrode is placed at the angle of the left scapula and the left leg electrode on the left leg.

‡In addition to CB, CR was taken. Occasionally this may be slightly greater in amplitude than CB.

§Three of these patients came to necropsy, which revealed extensive infarction involving both the anterior and posterior wall of the left ventricle.

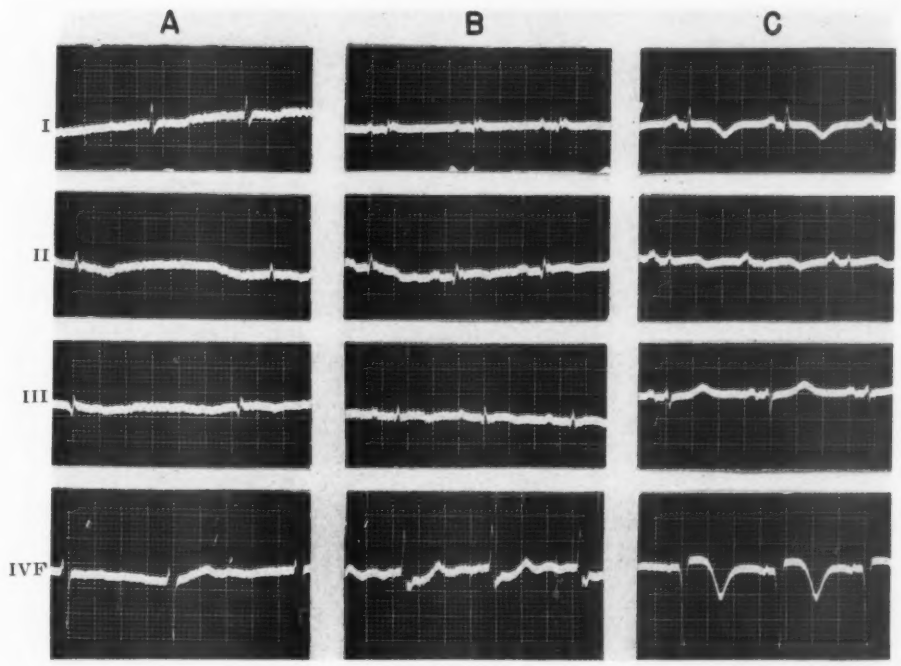


Fig. 1.—Note low voltage in limb leads, normal voltage in precordial leads. (*A*) A.B., aged 53. Arteriosclerotic cardiovascular disease, congestive failure with edema. (*B*) A.S., aged 83. Arteriosclerotic cardiovascular disease, posterior myocardial infarction, slight edema. (*C*) A.S., aged 70. Recent anterior infarction, no edema.

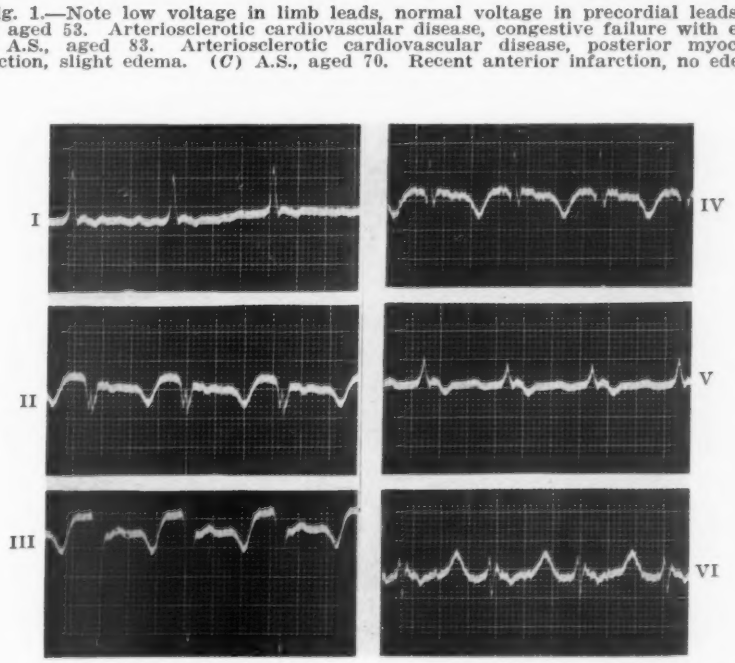


Fig. 2.—Shows the marked difference in voltage between IVB reversed (old Lead IV) and IVF reversed (old Lead V). F.S., aged 54. Anterior myocardial infarction. Note the high voltage of the QRS in Lead IV (reverse of IVB) and low amplitude in Lead V (reverse of IVF). This figure illustrates the importance of taking IVB before stating that the amplitude of the precordial lead is low.

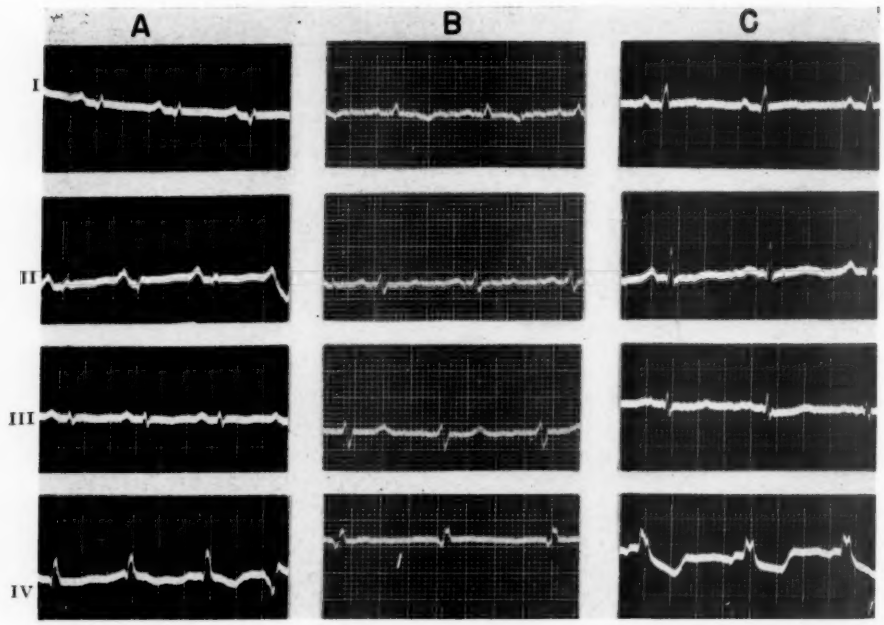


Fig. 3.—(*A*) Case 6: (Table I) Rheumatic heart disease, congestive failure. (*B*) Case 15: (Table I) Anterior myocardial infarction (chronic stage), arteriosclerotic heart disease, slight edema. (*C*) Case 8: (Table I) Recent anterior myocardial infarction, no edema. The precordial lead is IVB reversed (old Lead IV).

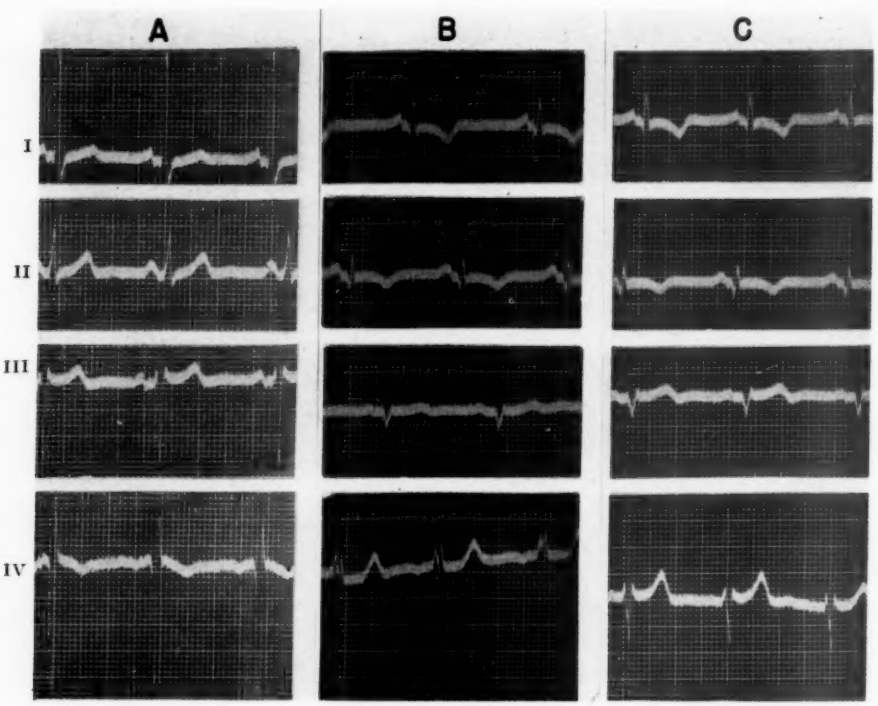


Fig. 4.—Case 2: (Table I) Male, aged 52. (*A*) Oct. 14, 1933. Diabetes, generalized arteriosclerosis. (*B*) Feb. 12, 1934. Patient developed acute coronary occlusion involving the anterior, and, later, the posterior wall of the left ventricle. Note the low amplitude in all leads, particularly old Lead IV (IVB reversed). Compare with (*A*). (*C*) Mar. 30, 1934. After his general condition had improved, some healing had taken place. Note increased voltage in Lead IV (reverse of IVB).

voltage. In the three remaining cases, the limb leads (except for low voltage) were within normal range, but in two of these there were abnormalities in the precordial leads. Therefore, in this series, electrocardiographic changes, aside from the low voltage, were observed in almost all the cases.

In an attempt to ascertain further the significance of low voltage in chest leads, we have also studied certain other groups of patients.

In Table II are shown the data on fifty patients who showed low voltage in the limb leads, but normal voltage in the chest leads.*

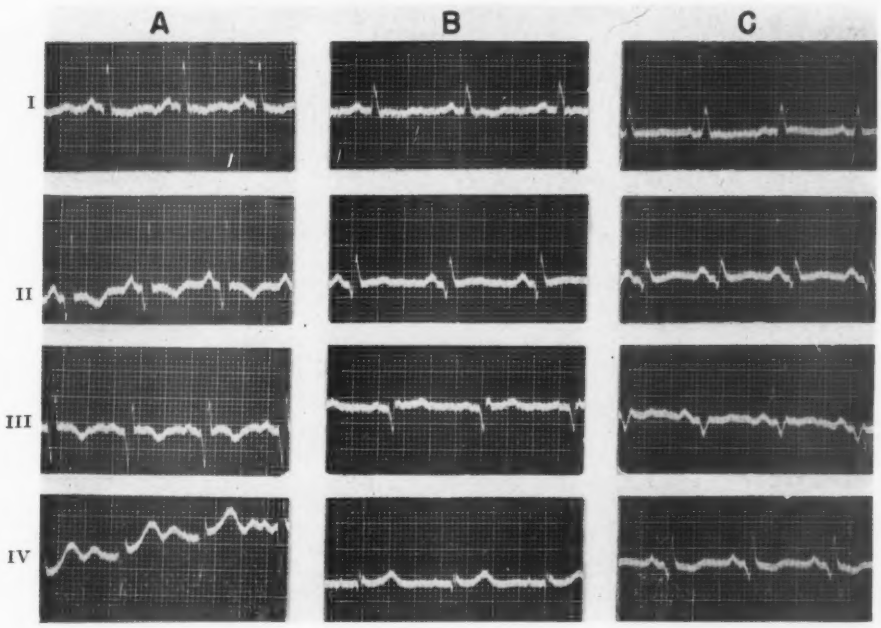


Fig. 5.—Case 16: (*A*) Jan. 25, 1935. Subsequent to posterior myocardial infarction. (*B*) April 1, 1935, two days after severe attack of precordial pain. Note low voltage in Lead IV. (*C*) May 29, 1936. Improvement in general condition. Note increase in voltage of QRS in Lead IVB reversed (old Lead IV). Autopsy revealed anterior and posterior infarction.

The severity of the myocardial damage in this group was much less marked than in the first. Only eighteen patients (36 per cent) had severe myocardial damage, as compared to 100 per cent in the previous group. Moreover, seventeen (34 per cent) had either normal hearts or slight myocardial damage, and fifteen (30 per cent) had a moderate grade of myocardial disease. Only thirteen patients (26 per cent) had myocardial infarction in this group, as compared to eleven (55 per cent) in the group with low voltage in both limb and precordial leads. In the group with low voltage in both limb and precordial leads, edema was

*It should be remembered that these electrocardiograms were taken on patients with suspected myocardial disease, in the medical wards. The percentage of myocardial disease in these cases of low voltage in limb leads might have been lower, had a different method of selection, such as was used in the series of Willius and Killins,[2] been applied.

TABLE 1

SUMMARY OF CASES OF LOW QRS VOLTAGE IN BOTH DIRECT AND INDIRECT LEADS*

| CASE NO. | AGE | SEX | CHANGES OTHER THAN LOW VOLTAGE | EDEMA | CARDIAC DIAGNOSIS | GRADES OF MYOCARDIAL DISEASE | OUTCOME |
|---|---|---|---|---|---|---|---|
| 1 | 64 | M | $T_1$ inverted; QRS slurred and notched in all 3 leads; LAD | Slight | Arteriosclerotic heart disease. Cardiac decompensation | Severe | Improved |
| 2 | 49 | M | $T_{1 \text{ and } 2}$ inverted and cove-shaped; $T_4$ inverted; $Q_{2 \text{ and } 3}$ present; LAD; $R_4$ absent | No | Arteriosclerotic heart disease. Chronic ant. and recent post. myocar. infarc. | Severe | Improved |
| 3 | 37 | F | T flattened in all 3 leads; ventric. extrasystoles | Moderate | Rheumatic heart disease. Cardiac decompensation | Severe | Died |
| 4 | 42 | M | $T_{1 \text{ and } 2}$ inverted; LAD | Slight | Syphilitic heart disease. Cardiac decompensation. | Severe | Improved |
| 5 | 74 | F | $T_{1 \text{ and } 2}$ flat; $S\text{-}T_{1 \text{ and } 2}$ depressed; $S\text{-}T_3$ elevated; $Q_{2 \text{ and } 3}$ present; LAD; $R_4$ absent | Marked | Arteriosclerotic heart disease. Chronic ant. myocar. infarc. Acute post. myocar. infarc. | Severe | Died (autopsy) |
| 6 | 28 | M | T flat in all leads; frequent ventric. extrasystoles | Marked | Rheumatic heart disease. Cardiac decompensation | Severe | Died |
| 7 | 60 | M | $T_{1 \text{ and } 2}$ inverted; LAD; $R_4$ absent | Marked | Arteriosclerotic heart disease. Cardiac decompensation. Chronic ant. myocar. infarc. | Severe | Died |
| 8 | 65 | M | $T_1$ flat; $S\text{-}T_1$ elevated; $S\text{-}T_4$ elevated; $R_4$ absent | No | Arteriosclerotic heart disease. Acute ant. myocar. infarc. | Severe | Improved |
| 9 | 62 | M | Q present in all 3 leads; $S\text{-}T_4$ elevated; $R_4$ absent | No | Arteriosclerotic heart disease. Acute ant. myocar. infarc. | Severe | Died |
| 10 | 64 | M | T flat in all 3 leads | Moderate | Tuberculous pericarditis. Congestive failure | Severe | Improved |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 11 | 61 | M | $T_1$ inverted; $T_4$ large and inverted; $R_4$ absent | No | Arteriosclerotic heart disease. Acute and chronic myocar. infarc. | Severe | Improved |
| 12 | 66 | M | $T_{2 \text{ and } 3}$ inverted; S-$T_1$ elevated; S-$T_4$ elevated; $R_4$ absent | No | Arteriosclerotic heart disease. Acute ant. myocar. infarc. | Severe | Died |
| 13 | 67 | M | $T_{2 \text{ and } 3}$ inverted; S-$T_1$ depressed; S-$T_4$ elevated; $R_4$ absent | No | Arteriosclerotic heart disease. Chronic post. myocar. infarc. Acute ant. myocar. infarc. | Severe | Died (autopsy) |
| 14 | 53 | M | T flat in all leads; S-$T_{2 \text{ and } 3}$ depressed; PR interval prol. (0.24 sec.) | No | Arteriosclerotic heart disease | Severe | Died |
| 15 | 39 | M | $T_1$ inverted; $T_4$ slightly inverted; LAD; $R_4$ small | Slight | Arteriosclerotic heart disease. Cardiac decompensation. Chronic ant. myocar. infarc. | Severe | Died |
| 16 | 53 | M | $T_1$ inverted; $T_2$ flat; $T_4$ inverted; $Q_{2 \text{ and } 3}$ present; $R_4$ absent | No | Arteriosclerotic heart disease. Chronic post. myocar. infarc. Acute ant. myocar. infarc. | Severe | Died (autopsy) |
| 17 | 61 | M | T flat in all leads; S-$T_{1 \text{ and } 2}$ depressed; ventric. extrasystoles; PR prol. (0.24 sec.) | Moderate | Arteriosclerotic heart disease. Cardiac decompensation | Severe | Improved |
| 18 | 50 | F | $T_{1 \text{ and } 2}$ low; $Q_3$ present | No | Arteriosclerotic heart disease. | Severe | Improved |
| 19 | 62 | M | $T_1$ flat; S-$T_4$ elevated; $Q_3$ present; $R_4$ absent | No | Arteriosclerotic heart disease. Chronic post. myocar. infarc. Acute ant. myocar. infarc. | Severe | Improved |
| 20 | 62 | M | $T_1$ flat; $S_2$ prominent; LAD | No | Arteriosclerotic heart disease | Severe | Died |

*The description of the change in the precordial leads is given according to the new method of applying the electrodes.[9]

TABLE II

CARDIAC CONDITIONS IN 50 CONSECUTIVE CASES OF LOW VOLTAGE IN LIMB LEADS WITH NORMAL VOLTAGE IN PRECORDIAL LEADS

| | CASES | |
|---|---|---|
| Arteriosclerotic heart disease (except acute coronary occlusion) | 21 | (42 per cent) |
| Acute coronary occlusion | 12 | (25 per cent) |
| Rheumatic heart disease | 4 | ( 8 per cent) |
| Syphilitic heart disease | 1 | ( 2 per cent) |
| Congenital heart disease | 1 | ( 2 per cent) |
| Pericarditis | 5 | (10 per cent) |
| Normal heart | 5 | (10 per cent) |

observed clinically in nine cases (45 per cent); in the group with low voltage only in the limb leads, it was observed in thirty cases (60 per cent).

Since pericarditis, especially with effusion, is occasionally associated with low voltage of the QRS complex,[10] the electrocardiograms of seventy-seven patients with pericardial disease of various types and etiologies were studied from the standpoint of voltage (Table III).

TABLE III

VOLTAGE OF THE QRS COMPLEX IN 77 CASES OF PERICARDIAL DISEASE

| | |
|---|---|
| *Normal voltage of QRS in limb and precordial leads* | |
| Pericardial effusion (moderate) | 21 cases |
| Other types of pericardial disease | 37 cases |
| *Low voltage in limb leads, normal voltage in precordial leads* | |
| Pericardial effusion (moderate) | 7 cases |
| Other types of pericardial disease | 11 cases |
| *Low voltage in limb and precordial leads* | |
| Tuberculous pericarditis with effusion, and thickened pericardium | 1 case |

From the figures in Table III, it is apparent that pericardial effusion which is moderate in degree (approximately 500 c.c.) is not, per se, a cause of low voltage in the limb leads. Of fifty-eight patients with pericardial disease who showed normal voltage, twenty-one (36 per cent) had effusion, whereas of eighteen cases of low voltage in the limb leads with normal voltage in the precordial leads, pericardial effusion was present in only seven (38 per cent). In a total of twenty-nine cases of pericardial effusion, low voltage was present in eight, or 27 per cent; in some of these, other factors, e.g., peripheral edema, were present, and may have had a part in lowering the voltage.

The low voltage in both limb and precordial leads in the single case of tuberculous pericarditis was probably caused by the markedly thickened, adherent pericardium. The effusion was slight, loculated, and limited to the lower right portion of the pericardial sac.

Also, for purposes of comparison, we examined the electrocardiograms of 300 normal college students. In none was there low voltage of the QRS complexes in either the limb or precordial leads.

The data presented above indicate that although low voltage in the limb leads alone may be observed when the heart is either normal or

diseased, the presence of low voltage in both the precordial and limb leads is almost always associated with considerable myocardial damage.

## DISCUSSION

*Factors That Affect the Voltage of Limb Leads.*—The voltage of the QRS complex is, of course, primarily dependent upon the electromotive force developed by the contracting heart muscle. As registered in the electrocardiogram, however, the voltage of these waves is a resultant of the difference in potential of tissue underneath two electrodes which are quite widely separated from each other, and sometimes distant from the heart. Although a deficiency in electromotive force incident to heart disease may undoubtedly be a cause of low voltage, it is quite obvious that many other factors may play a part, even when the electromotive force at its point of origin, the heart, may be quite normal.

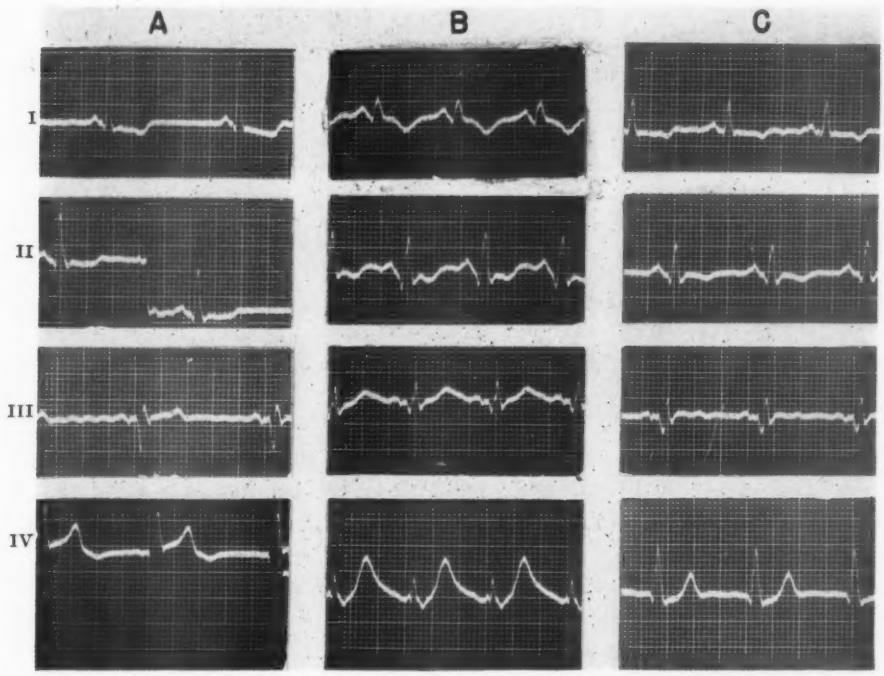


Fig. 6.—Case 11: (*A*) Oct. 19, 1936. History of old infarction. (*B*) Nov. 7, 1936. Patient experienced an attack of precordial pain. Diagnosed anterior infarction. Note diminution of voltage of QRS in Lead IVB reversed (old Lead IV). This is smaller than that noted in the limb leads.* (*C*) Nov. 17, 1936. With improvement, voltage has increased.

*In a few cases, as in Fig. 6 (*B*), we have noted a slightly lower voltage in the precordial than in the limb leads. This is apparently infrequent.

Eyster and his co-workers[11] and Katz and his co-workers[12, 13] have shown that the current produced by the heart is not conducted uniformly to the surface. Some regions of the heart which are in contact with good conductors have an advantage over those portions which are not. For example, Katz, et al.,[14] in summarizing their view on this subject, state that the caudad regions of the right auricle, right ventricle,

and left ventricle, and those in contact with the posterior paravertebral muscle mass will have a greater effect on the standard three-lead electrocardiogram; the portions of the heart in contact with the anterior chest wall will have a less important influence because they are surrounded by lung which is so thick that little current is conducted from this region.

In certain cases, as pointed out by Wilson,[15] low voltage in the limb leads may be accidental, and be caused by the fact that the potential differences produced by one part of the heart are almost exactly neutralized by those produced in other parts. Wolferth and Wood[16] believe that the limb lead voltage may be low as a result of neutralization of potentials at the surface of the body.

Voltage variations in the normal subject may be caused by many additional factors, e.g., the habitus of the individual, differences in the position and shape of the heart, the relation between the size of the heart and the size of the thoracic cage, and obesity. These factors could all be operative in entirely healthy persons; they offer a fairly satisfactory explanation of low voltage in the limb leads of persons with essentially normal hearts.

There are a number of pathologic states that might further affect the voltage of the QRS complexes.

*Factors Which Modify Voltage of Limb Leads in Pathologic States.*—In addition to the factors which tend to modify the voltage in the normal subject, the voltage in the presence of myocardial damage will apparently be affected in two chief ways: (a) by a modification in the source of potential, the heart, and (b) an alteration in the conduction of the heart current to the surface of the body.

An alteration in the electrical potential produced in the heart could be the result of disease of the heart muscle. An alteration in the conduction to the surface of the body of the current produced in the heart could result from a modification of the structures that normally surround the heart and act as conductors of its current. Among these are (a) air containers, which are poor conductors,[15, 17] (b) fluid, which, because it is a good conductor, will shunt the heart current so that a smaller amount will reach peripherally-placed electrodes,[13, 15] and (c) solid structures; thick adhesions, which are relatively avascular, will further insulate the heart, but pneumonic consolidation should act as a good conductor.[5, 14]

In any event, we often encounter low voltage of the QRS complexes in association with massive pericardial effusion, air in the pericardium, thick adhesions around the heart, pneumonic consolidation, edema of the lung, pleural effusion, pneumothorax, generalized peripheral edema, emphysema, dehydration, and conditions associated with profound disturbances of the electrolyte content of the blood.

A combination of these factors, cardiac as well as extracardiac, may operate to produce low voltage in a given case.

*Low Voltage in Chest Leads.*—The various factors which may contribute to the production of low voltage in indirect leads do not apparently affect chest leads. Although low voltage may be observed in the limb leads of normal subjects, the precordial leads show normal voltage. Even in the presence of myocardial disease, one generally finds normal voltage in the chest leads when the voltage in the limb leads is notably low. As we have stated, we were able to collect only twenty well-studied instances in which the voltage in the chest lead was low.

In precordial leads, the form of the electrocardiogram depends upon factors other than those which affect limb leads. In the former, the exploring electrode is much closer to the heart, and therefore registers curves which more closely resemble the electrogram.

Although most of the factors mentioned above will tend to produce low voltage in the limb leads, few of them affect the voltage of the precordial leads. By placing the electrode over the precordium, the factors of edema, pleural effusion, pericardial effusion, etc., interfere little with the registration of the voltage.

Experimentally, Goodman[18] has shown that edema, unless it is present in the subcutaneous tissues of the chest region, will not affect the voltage of the QRS complexes of the precordial leads. Clinically, edema seldom involves this region. The only other factor which is likely to affect the conduction of the heart current in precordial leads is the presence of fluid or abnormal air-containing structures between the heart and the anterior chest wall; the latter is a condition that is certainly rare. That precordial lead voltage may be affected by bilateral, massive pleural effusion is illustrated by the following case: In a patient 59 years of age, with severe degenerative heart disease, low voltage was present in the limb leads and precordial leads ($CF_{3,4,5}$, $CR_{3,4,5}$, $CB_{3,4,5}$). On removal of fluid from the right and left pleural sacs (30 oz.), the voltage in the precordial leads changed from 2 mm. to 5 mm. This change was recorded only in the CB and CR leads.

Since the transmission to the chest wall of the current produced in the heart is usually good, apparently the main factor which is likely to cause low voltage in the precordial leads is a decrease in the voltage produced by the heart muscle as a result of severe myocardial disease involving relatively large portions of the myocardium. This would explain the extremely low voltage in these leads in cases of anterior and posterior infarction, and the high incidence of severe myocardial disease in the group of patients reported here. That this need not be a permanent condition is illustrated in Fig. 5; in this case, anterior infarction superimposed upon an old posterior infarction resulted in low voltage. With healing of the infarct, the voltage again became normal.

If this concept is correct, it would help to establish three important points: (a) The factors which tend to produce low voltage in the limb leads do not necessarily affect the voltage of the precordial leads. (b) Low voltage in the precordial leads is usually the result of inherent

disease of the heart muscle; it is infrequently the result of extracardiac factors.* (c) Low voltage in the precordial leads is almost always associated with a severe grade of myocardial damage.

## SUMMARY AND CONCLUSIONS

Of twenty patients who had low voltage in both the precordial and limb leads, all showed evidence of severe myocardial damage. In this group there were eleven cases of myocardial infarction, in five of which there was involvement of both the anterior and posterior wall of the left ventricle. The severity of myocardial disease was considerably less in a group of fifty consecutive cases in which the voltage was low in the limb leads and normal in the precordial leads. There were no cases of combined anterior and posterior infarction in this group. The incidence of low voltage in pericardial disease, both with and without effusion, is mentioned for comparison. No instances of low voltage were observed in a control group of 300 students.

One should not rely upon a single precordial lead for a diagnosis of low voltage. In addition to the CF leads (3, 4, 5), CB and CR leads should be taken.

The factors responsible for normal voltage and their modifications in various diseases are discussed. Since low voltage in the precordial leads is the result of factors other than those that produce it in the limb leads, the combination of low voltage in both is a more certain evidence of myocardial disease than the latter alone.

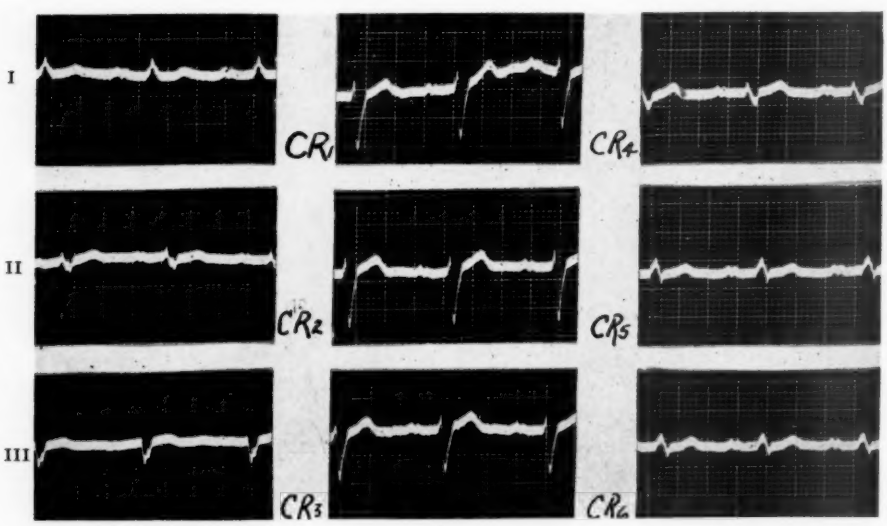


Fig. 7.—Low voltage in some chest leads with normal voltage in others. In the limb leads and in the generally used chest leads, $CR_{3, 4, \text{ and } 5}$, the voltage is low. It is normal, however, in chest leads $CR_{1, 2, \text{ and } 3}$. It is our opinion that the chest lead voltage should not be called "low" in such a tracing.

*In our series we have encountered but one case, mentioned above, in which the low voltage in the precordial leads was, to some degree, the result of massive pleural effusion; some of the fluid was probably situated between the heart and anterior chest wall. In this instance, severe myocardial disease was also present.

## ADDENDUM

Since this paper was accepted for publication, another paper dealing with the same subject has been published by Leach, Reed, and White (American Heart Journal **21**: 551, 1941). The difference in the conclusions expressed in the two papers may, in our opinion, result from the fact that Leach, Reed, and White used only one chest lead, so far as we can judge, whereas we used several. It has been our experience that one chest lead (frequently a conventionally used one) may yield low voltage curves, whereas chest leads from other precordial areas may give curves of normal voltage (Fig. 7). Such instances we have not considered to be examples of low chest lead voltage. It is our opinion that the voltage of the chest leads can be considered to be low only after it had been shown to be present in several chest leads.

## REFERENCES


1. (a) Oppenheimer, B. S., and Rothschild, M. A.: The Value of the Electrocardiogram in the Diagnosis and Prognosis of Myocardial Disease, Tr. A. Am. Phys. **39**: 247, 1924.
   (b) White, P. D., and Burwell, S. C.: The Clinical Significance of Changes in the Form of the Electrocardiogram, Med. Clin. N. Amer. **4**: 1839, 1920-1921.
   (c) Clerc, A., and Bascourret, M. P.: Les Anomalies des complexes ventriculaires electriques et leur importance pronostique dans les cours de l'insuffisance cardiaque, Rev. de med. **41**: 587, 1924.
   (d) Pardee, H. E. B., and Master, A. M.: Electrocardiogram and Heart Muscle Disease, J. A. M. A. **80**: 98 (Jan. 13), 1923.
2. Willius, F. A., and Killins, W. A.: The Occurrence and Significance of Electrocardiograms of Low Voltage, Arch. Int. Med. **40**: 332, 1927.
3. Katz, L. N., and Kissin, M.: A Study of Lead IV, AM. HEART J. **8**: 595, 1933.
4. Shipley, R. A., and Halloran, W. R.: The Four-Lead Electrocardiogram in 200 Normal Men and Women, AM. HEART J. **11**: 325, 1936.
5. (Personal Observations of the Authors.)
6. Sprague, H. B., and White, P. D.: The Significance of the Electrocardiograms of Low Voltage, J. Clin. Investigation **13**: 109, 1926.
7. Pardee, H. E. B.: The Clinical Aspects of the Electrocardiogram, New York, 1928, Paul Hoeber.
8. Wood, F. C., Bellet, S., McMillan, T. M., and Wolferth, C. C.: Electrocardiographic Study of Coronary Occlusion. Further Observations on the Use of Chest Leads, Arch. Int. Med. **52**: 752, 1933.
9. Standardization of Precordial Leads, AM. HEART J. **15**: 107, 1938.
10. Oppenheimer, B. A., and Mann, H.: An Electrocardiographic Sign in Pericardial Effusion, Proc. Soc. Exper. Biol. and Med. **20**: 421, 1923.
11. Eyster, J. A. E., Maresh, F., and Krasno, M. R.: The Nature of the Electrical Field Around the Heart, Am. J. Physiol. **106**: 574, 1933.
12. Katz, L. N., Gutman, I., and Ocko, F. H.: Alterations in the Electrical Field Produced by Change in the Contacts of the Heart With the Body, Am. J. Physiol. **116**: 302, 1936.
13. Katz, L. N., Sigman, E., Gutman, I., and Ocko, F. H.: The Effect of Good Electrical Conductors Introduced Near the Heart on the Electrocardiogram, Am. J. Physiol. **116**: 343, 1936.
14. Katz, L. N. et al.: Concerning a New Concept of the Genesis of the Electrocardiogram, AM. HEART J. **13**: 17, 1937.
15. Wilson, F. N.: The Distribution of the Potential Differences Produced by the Heart Beat Within the Body and at Its Surface, AM. HEART J. **5**: 599, 1930.
16. Wolferth, C. C., and Wood, F. C.: The Prediction of the Amplitude and Direction of Waves in the Precordial Leads CR, CL, and CF on the Basis of the Limb Lead Findings, AM. HEART J. **20**: 12, 1940.
17. Katz, L. N., and Korey, H.: Manner in Which Electric Currents Generated by the Heart Are Conducted Away, Am. J. Physiol. **111**: 83, 1935.
18. Goodman, M.: Effect of Edema on the Amplitude of the Electrocardiographic Waves, AM. HEART J. **10**: 269, 1934.

# THE AORTIC VALVULAR LESION ASSOCIATED WITH THE AUSTIN FLINT MURMUR

BENJAMIN A. GOULEY, M.D.
PHILADELPHIA, PA.

ONE explanation of the mechanism of the Austin Flint murmur which is acceptable to many clinicians is that blood regurgitating through a damaged aortic valve strikes against the anterior mitral curtain and pushes it laterally into the auriculoventricular blood stream. Thus, a functional obstruction is created at the mitral valve. The anterior mitral leaflet, which is displaced from its usual mural position in diastole, now hangs suspended between two downflowing streams of blood and is impinged on by both, and this sets up the vibrations which cause the rumbling presystolic apical murmur of aortic regurgitation. This explanation is a summary of many views, all of which, although they differ more or less in detail, take into consideration the essential factor of aortic regurgitation and the likely secondary factor of functional mitral valvular obstruction.

A rather small minority of patients with aortic regurgitation have a Flint murmur; this fact was apparent to the early investigators, but was never fully accounted for. The above explanation of the mechanism of the murmur, like all others, therefore remains incomplete. It is likely that some anatomic or physiologic difference marks off those with the murmur from the majority of patients with aortic regurgitation. Until recently, detailed investigation of the changes in the aortic leaflets in such cases was seldom attempted; most pathologists were satisfied when they found that the mitral valve was normal in the presence of aortic regurgitation.

It has generally been thought that the Flint murmur is due to a lesion involving the posterior aortic leaflet. This assumption was largely based on theoretical considerations, until Herrmann produced aortic regurgitation in dogs by perforation and laceration of the posterior aortic leaflet. After the operation, many of these dogs (36 per cent) had a diastolic apical murmur and a diastolic apical thrill. Such signs did not appear in the few dogs whose right or left anterior aortic leaflets were damaged without injuring the posterior cusp. An experimental basis was thus established for the Flint murmur. This experimental lesion, however, is not identical with the lesions which we have constantly noted in patients who came to necropsy. The structural change to which we refer consists of two lesions, namely, (1) a peculiar deformity of the right anterior leaflet, and (2) a thickening

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of the anterior (aortic) mitral curtain, especially of its lower portion, on the ventricular aspect, where the chordae tendineae are attached. The lesion of the right aortic leaflet is the more important; that of the anterior mitral curtain is secondary, and is the result of the constantly recurring impact of the regurgitant stream on that curtain.

The right aortic leaflet in ten cases, of which 5 will be discussed here, presented a concave, cup-shaped deficiency of its inner portion, i.e., the portion of the leaflet adjacent to commissure No. 2 (connecting the right anterior and the posterior aortic leaflets). This inner portion of the right aortic leaflet sagged, and the free margin pouched or drooped outward into the ventricular lumen. In one case the entire leaflet had weakened and was stretched, and its free margin was rolled and everted. In this instance, the inner corner of the leaflet was notably more seriously involved, and sagged to a lower level. In all cases this cup-shaped depression faced more or less laterally in the direction of the anterior mitral curtain. The other leaflets were either normal or involved in what often was a syphilitic process, that is, they were retracted in variable degree as is commonly the case in that type of valvulitis.

The second feature, namely, the thickening of the anterior mitral curtain on its ventricular aspect, was variable in its development. In some cases the lower half of the curtain, including the site of attachment of the chordae tendineae, showed an almost uniform increase in thickness and opacity (Fig. 1). In most instances, this was notable at the inner and usually the lower portion of the curtain, and the endocardial sclerosis also involved the mural endocardium of the adjacent ventricular septum. In one instance this thickening took on unusual aspects, giving rise to spindle-shaped and cylindrical enlargement of the chordae tendineae at the point of their attachment with the mitral curtain (Fig. 3). Possibly masses of fibrin had originally been deposited in these areas. In two cases, endocardial ridging down along the ventricular septum suggestively marked out a diagonal path leading from the damaged right aortic leaflet. Time is undoubtedly a factor in producing these endocardial changes on the anterior mitral curtain. They almost certainly are the result of friction, and it is likely that in some cases death ensues before marked changes occur.

Of the ten patients who presented this type of aortic valvular deformity, nine were men and all were between the ages of 30 and 45 years. The majority of these patients had syphilitic cardiovascular disease. In one case there was a complicating subacute bacterial mitral endocarditis, which we believe had no connection with the aortic valvular deformity, and in two the aortic lesion was due solely to rheumatic disease.

## REPORT OF CASES

CASE 1.—J. S., a negro, aged 38 years, was admitted to the Philadelphia General Hospital on the medical service of Dr. W. E. Robertson, complaining of

paroxysmal dyspnea and edema of the legs. There was palpitation, but no precordial pain. Examination revealed basal pulmonary congestion, ascites, edema of the legs, and a blood pressure of 200/0. He had an aortic diastolic murmur which was transmitted down the left border of the sternum. In the apical area, in the fifth and sixth intercostal spaces, beyond the midclavicular line, there was a rumbling presystolic murmur, followed by a short systolic murmur. The heart was greatly enlarged to the left, the peripheral signs of aortic regurgitation were well developed, and the blood Wassermann and Kahn reactions were strongly positive. The clinical diagnosis was syphilitic cardiovascular disease, with aortic regurgitation and a Flint murmur.

Necropsy showed a heart weighing 850 grams, a markedly enlarged left ventricle, syphilitic aortitis, and slight widening of commissure No. 2. The right anterior leaflet extended out into the valvular lumen more than the others, which were slightly retracted, and it showed a distinct tendency to pouch and sag at its inner corner (Fig. 1). The free edge at this corner was thickened and dropped downward, forming a depressed cupping. No local sagging was noted in the other aortic leaflets. The anterior mitral leaflet showed definite thickening and an increased opacity of the lower portion on the ventricular aspect. The upper ends of the chordae tendineae were thickened at their points of attachment. However, the mitral valve, when viewed from its inner aspect, was entirely normal.

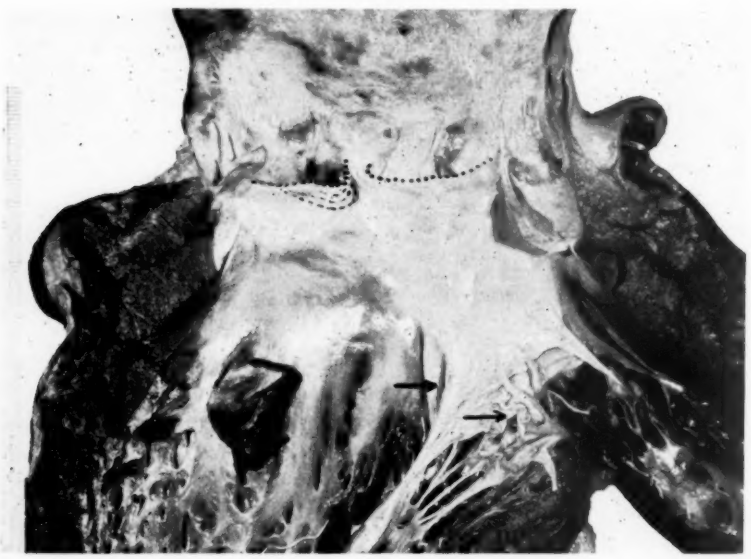

Fig. 1.—Case 1. The inner portion of the right anterior aortic leaflet pouches out into the ventricular lumen in the direction of the anterior mitral curtain. The free margin of this part of the leaflet was slightly rounded and lipped. The lower portion of the anterior mitral curtain was moderately and uniformly thickened, as were the chordae tendineae at their points of attachment. The mitral valve, viewed from its inner aspect, was normal.

Case 2.—R. R., a negro, aged 30 years, was admitted March 29, 1934, to the Philadelphia General Hospital on the medical service of Dr. T. Schnabel, complaining of shortness of breath and swollen ankles. Cardiac failure had first been noticed in March, 1931, since which time the patient had suffered repeated attacks of dyspnea, and eventually developed orthopnea and dizziness. There was a history of syphilitic infection in 1920, for which the patient had received treatment for nine months.

Examination showed a young, well-nourished man, with a blood pressure of 200/50 in both arms, and with all the peripheral signs of aortic regurgitation. The heart was greatly enlarged; the left border was in the axilla in the fifth and sixth intercostal spaces. No thrills were palpable. The blood and spinal fluid Wassermann reactions were negative. Nevertheless, mild antisyphilitic treatment was administered. When the patient was readmitted to the hospital the serologic reactions were strongly positive (4 plus). Auricular fibrillation developed and resulted in fatal cerebral embolism on October 18, 1935.

Necropsy revealed a huge heart, weighing 980 grams; the left ventricle was markedly dilated. Aside from relative insufficiency, the mitral valve was normal, as were the tricuspid and pulmonic. There was no widening of the aortic commissures despite the presence of syphilitic aortitis. The aortic leaflets were slightly thickened; only the right aortic, however, showed a rolling of its free edge, in addition to which there was a sagging of the inner portion of the leaflet. On the ventricular aspect of the anterior mitral curtain there was a patchy, irregular thickening, with numerous, small, pinkish-gray elevations of the endocardial surface.

CASE 3.—A. G., a negro, aged 45 years, was admitted August 14, 1935, to the Philadelphia General Hospital on the medical service of Dr. Truman Schnabel, complaining of dyspnea which had begun eighteen months before as "asthma."

Examination revealed orthopnea, venous hypertension, and a flat percussion note and tubular breathing over the upper lobe of the right lung. The entire chest was filled with râles, and this precluded satisfactory examination of the heart. On one occasion a diastolic apical murmur was heard. The apical beat was in the sixth intercostal space in the anterior axillary line. The blood Wassermann reaction was strongly positive (4 plus). Death occurred suddenly on August 18.

Necropsy showed a greatly dilated, bowl-shaped left ventricle. There was a hinge valve deformity* of the right anterior aortic leaflet. The inner portion of this thickened leaflet showed an exaggerated sagging which formed a low, cup-shaped depression. The posterior and left anterior leaflets were entirely normal. The inner and lower aspect of the anterior mitral curtain (ventricular side) was thickened and ridged. The mitral valve itself was normal.

The aorta was the seat of a diffuse, syphilitic aortitis, and there was an aneurysm of the horizontal arch, involving the innominate artery.

Note: Although the diastolic apical murmur could not be clearly defined as an Austin Flint murmur, the post-mortem observations almost certainly identify it as such.

CASE 4.—P. M., a negro chauffeur, aged 39, was admitted to the Philadelphia General Hospital on the service of Dr. F. Kalteyer, October 19, 1939, complaining of chills and nosebleeds. Severe, sharp precordial pain had been experienced with increasing frequency, and shortness of breath and great weakness were noted one week before hospitalization. He had had a penile lesion at the age of 18.

Physical examination revealed a very anemic, but well-nourished man who was slightly dyspneic and had moderate clubbing of the fingers. The blood pressure was 120/58. A to-and-fro murmur was heard at the aortic area. Diastolic and systolic murmurs were heard in the fifth intercortal space, and replaced both heart sounds. The diastolic rumble increased in intensity up to the first sound, merging with it to form a long and almost continuous mitral murmur.

*"Hinge valve" is a term applied in the Philadelphia General Hospital to the strikingly everted right aortic leaflet that is often accompanied by high-pitched, musical, diastolic murmurs.[1] Such a murmur may have been obscured in this case by the noisy respiration.

Death occurred shortly after admission, before the serologic studies were completed.

Necropsy showed a heart weighing 450 grams, with a large left ventricle of globular shape which was more dilated than hypertrophied. The anterior mitral leaflet on its auricular aspect was covered in its upper portion (the free margin was not involved) by an ulcerating thrombotic mass (subacute bacterial endocarditis, *Streptococcus viridans*). Viewing the anterior mitral curtain on its ventricular aspect, it was noted that the ulcerative process had just about broken through the body of the leaflet. The upper portion of the curtain on this aspect showed some fibrinous deposit which extended up toward the base of the posterior aortic leaflet. The latter, however, was entirely normal.

The right anterior aortic leaflet sagged, especially its inner portion, which presented a cup-shaped deficiency (Fig. 2). The free edge was rolled and thickened. The posterior and the left anterior leaflets were normal, except possibly for a slight widening of the intervening commissure. There were marked thickening and opacity of the mural endocardium, extending from the weakened inner corner of the right aortic leaflet diagonally down and across the ventricular septum, and reaching the lowermost portion of the anterior mitral curtain, which, together


Fig. 2.—Case 4. The right anterior aortic leaflet shows marked sagging and cupping, especially its inner portion (*A*). The posterior leaflet is normal except for slight retraction at the commissure joining it with the left aortic leaflet, also despite the presence of fibrinous deposit reaching its base from the adjacent vegetative mitral endocarditis (*B*). Note marked sclerotic thickening (arrows) along lower portion of anterior mitral curtain and adjacent septal endocardium which is distinct from the acute fibrinous extension from the mitral lesion to the chordae tendineae. The sclerotic endocarditis is confined to a belt leading down diagonally from the damaged right aortic leaflet.

with its innermost chordae tendineae, shared in the sclerotic process. This sclerosis was evidently chronic, and independent of the ulcerative lesion high in the body of the anterior mitral curtain. It appeared to be sharply marked off, especially in its upper portion beneath the weakened right aortic leaflet, and thus suggestively outlined a track that was followed by the downflowing regurgitant blood stream.

Above commissure No. 2, and almost imperceptibly above commissure No. 3, there were small, slightly elevated, rather moist and translucent swellings of the intima of the aorta. Histologically, the aortic wall showed typical syphilitic changes in these areas.

Note: In this case of aortic regurgitation accompanied by a Flint murmur, the syphilitic aortic valvular disease was confined to the right aortic leaflet, giving rise to a characteristic deformity and a "directed" mural endocardial sclerosis marking the line of regurgitation. The posterior aortic leaflet was normal.

CASE 5.—A. H., aged 35 years, a white elevator operator, was admitted to the Philadelphia General Hospital March 23, 1940, on the service of Dr. P. Jump, complaining of shortness of breath. He had had rheumatic fever in 1935, but otherwise had been in good health until Christmas, 1939, when he became dyspneic, and soon thereafter he noted swelling of the ankles.

Examination revealed rheumatic heart disease. There was a marked presystolic murmur at the apex, followed by a short systolic murmur. This apparent mitral stenosis was accompanied by signs of aortic valvulitis, i.e., a short systolic and diastolic murmur were heard in the aortic area. The blood pressure was 140/70. Both lung bases were congested. Right-sided heart failure was evidenced by venous hypertension, an enlarged liver, and some edema of the legs. Fluoroscopic examination revealed a large left ventricle, a prominent pulmonary arterial salient, and hilar pulmonary congestion. The electrocardiogram showed prolongation of the P-R interval (.21 second) and notched P waves. Death was sudden on April 4, 1940.

Necropsy: Both ventricles were enlarged and hypertrophied, particularly the left.

There was, surprisingly, no mitral stenosis. The mitral valve was 12.5 cm. in circumference, so that there was apparently a relative insufficiency. There was very slight thickening at the free edge (Fig. 4); also, increased vascularity was noted at the base of the valve. The important changes were on the ventricular aspect of the anterior mitral curtain and in the right aortic leaflet. The latter exhibited a collapse fibrosis. The upper portion of the leaflet, including its free margin, had largely caved inward toward the aortic wall. Fibrous stiffening maintained this peculiar position. The median portion of the leaflet, leading to commissure No. 2, was most seriously involved; the upper line of the leaflet had practically disappeared, and was replaced by a marked concavity (Fig. 3). The other leaflets showed some thickening and were lightly fused to each other at the commissures, but they did not exhibit the collapse seen in the right anterior leaflet.

The lower portion of the anterior mitral curtain (ventricular aspect) showed a generally increased thickening and opacity, and, further up, the endocardial surface was ridged and irregularly roughened. Some of the more prominent ridges were almost horizontal, and their inner ends tipped upward in the direction of the membranous septum and the damaged right anterior leaflet.

The chordae tendineae were elongated, but, in addition, they showed, especially those streaming laterally, marked spindle-like thickening at the point of their insertion into the mitral curtain. These thickenings had a smooth surface and were all most prominent on the ventricular or aortic aspect of the curtain; in contrast, the mitral valve was practically normal in appearance when viewed from the auricular aspect.

## DISCUSSION

Flint[2] thought that functional mitral stenosis was the cause of the murmur, and, since his time, many suggestions have been made as to how and when such a situation would develop. Guiteras[3] stated that the mitral leaflets are not "floated upwards," as was suggested by

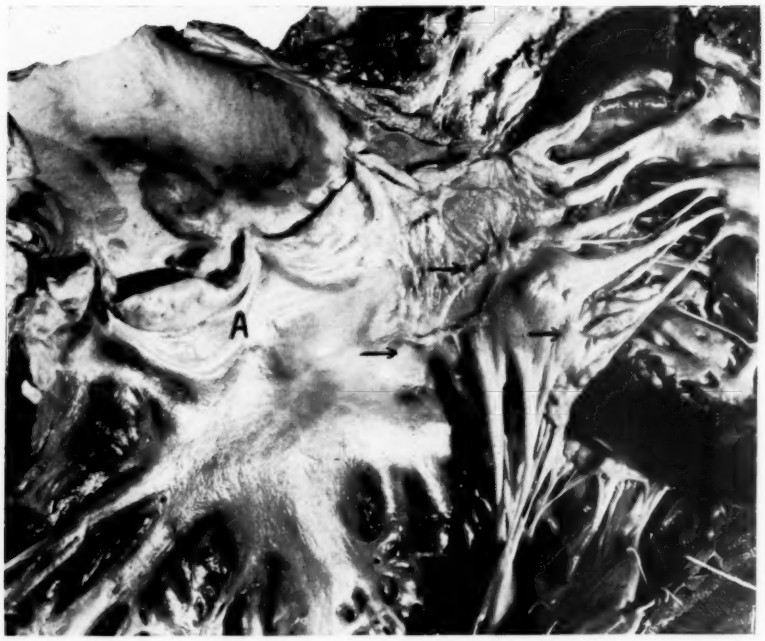


Fig. 3.—Case 5. Note marked deficiency and cupping of inner portion of right anterior aortic leaflet (*A*). Arrows mark sclerotic thickening and ridging of the anterior mitral curtain. Note spindle shape and bulbous thickening of the chordae tendineae at the points of insertion in the mitral leaflet. Posterior aortic leaflet is normal.

Fig. 4.—Case 5. The mitral valve is practically normal. There is slight thickening of the anterior mitral flap, and the bulbous thickening of the upper ends of the chordae tendineae which was so prominent on the ventricular aspect can barely be seen.

Flint, but are *actively driven* against the auricular blood flow by the "general arterial tension." Apparently he believed that the force striking against the mitral curtain, which diminished the valvular channel, did not derive directly from the regurgitant aortic stream, but was rather the result of the speedy filling of the ventricle from both the aorta and the auricle. J. C. Da Costa[4] believed that dilatation of the left ventricle was an essential factor, and that this displaced the anterior mitral curtain, making it tense and the target of two oppositely directed streams of blood. In this connection, it may be pointed out that, in almost every case, predominant aortic regurgitation is accompanied by dilatation of the left ventricle, but the Flint murmur is not universally present. Broadbent[5] said that the regurgitant aortic stream impinged on the anterior mitral curtain, causing it to vibrate; he appeared to be clearer on this point than his contemporaries, yet this also did not explain the *occasional* occurrence of the Flint murmur in aortic regurgitation. Finally, recent experimental work seems to indicate that the anterior mitral curtain is itself of little importance in the pathogenesis of the murmur; it acts merely as the transmitter of vibrations which are set up in the aortic leaflets.[6]

The importance of the associated aortic regurgitation has generally been recognized, but the relationship between the organic aortic lesion and the presumed functional mitral involvement has never been clear. The aortic valvular deformity herein described, the more or less well-developed changes on the ventricular aspect of the anterior mitral curtain, and the occasional tell-tale markings on the intervening ventricular septum constitute strong evidence, in our opinion, that the regurgitating blood is directed or "grooved" down and across the ventricular septum, forcing the anterior mitral curtain into the auriculoventricular current. We believe that this peculiar anatomic and physiologic variation of aortic regurgitation is in most instances the cause of the Flint murmur. If this is borne out by other observers, it will establish the validity of a functional mitral valvular stenosis.

The reason for the involvement of a precise part of a particular aortic leaflet (right anterior) is not clear. The constant location of this valvular defect in cases of varied etiologic origin suggests that a mechanical factor is of some importance. Possibly the point of maximum impact of the diastolic aortic recoil is, in some cases, at the inner corner of the right aortic leaflet; this point of greatest strain becomes evident when the valvular structure is undermined by inflammatory processes. Syphilitic valvulitis is common, whereas rheumatic or other infectious lesions are relatively uncommon. It appears that some destructive process incidental to infection, usually syphilitic, plays an important role. We have previously pointed out that the right anterior aortic leaflet was almost constantly involved in the "hinge-valve" lesion associated with musical diastolic murmurs, and that destruction of the supporting fibro-elastic "basket" of that leaflet by syphilis was a de-

termining factor in the subsequent valvular deformity.[1] It is probable that a similar inflammatory process is directed by some mechanical factor in the localization and development of the valvular deformity of the Flint murmur.

*The role of posterior valve leaflet lesions.*—The eccentric, cup-shaped depression of the right aortic leaflet occasionally occurs in the adjacent portion of the posterior leaflet as an associated lesion. We have not seen it there as the sole aortic valvular deficiency in cases featured by the Flint murmur. This is mentioned because the posterior leaflet is considered the site of lesions responsible for the murmur. It is conceivable that the murmur in some cases is caused by posterior leaflet changes which allow that leaflet to drag or flap, or in some way to hang out loosely in the lumen. In syphilitic aortic regurgitation, the most common type of heart disease with which the Flint murmur occurs, such lesions of the posterior leaflet are rare. Far more commonly this leaflet is shortened, thickened, and retracted toward the aortic wall, allowing *free* regurgitation and minimizing the possibility of abnormal vibration. In an occasional case of subacute bacterial endocarditis, ulceration and perforation at the base of the posterior aortic leaflet may provide a small aperture which allows diastolic leakage under pressure. This might well be a cause of marked vibration which would be easily transmissible to the anterior mitral curtain. We have not seen such a case,* and we believe that it is uncommon. It would constitute a clinical counterpart of the experimental lesion of Herrmann. We have not seen the left anterior aortic leaflet involved in this type of valvular deficiency. Regurgitation caused by a defect in this leaflet would scarcely touch the anterior mitral curtain with the heart tilted as it normally is in man.

It is interesting that, although syphilitic aortitis remains undoubtedly the chief cause of aortic valvular insufficiency in these cases, other types of heart disease are not excluded. This has been previously noted,[8] although seldom supported by necropsy confirmation. In Case 5 (A. H.), the history clearly implicated rheumatic fever, and serologic tests for syphilis were negative. The presystolic apical murmur was regarded unhesitatingly as a manifestation of advanced mitral stenosis. The Flint murmur is rare in rheumatic heart disease because isolated aortic regurgitation is not often encountered, and also because even moderate stiffening of the anterior mitral curtain by rheumatic inflammation would lessen the chance of vibration. Nevertheless, aortic valve insufficiency does occur sometimes rather acutely in children and in young adults in the course of rheumatic fever, before mitral stiffening has developed, and in such patients a Flint murmur may occasionally be heard.

In attempting to correlate changes in the aortic leaflets with the Flint murmur, it must be realized that other cardiac murmurs also have

*Herrmann's second case was apparently of this type.[6] Sansom[7] mentioned a case of Guiteras' which was featured by a congenital aperture in the posterior leaflet.

their origin in aortic regurgitation, and that confusion may develop if their identification is either incomplete or, as is sometimes the case, difficult. The ordinary, blowing, diastolic murmur of aortic regurgitation which is often transmitted down along the sternum is also not uncommonly heard in the axilla, unaltered and apparently directly propagated. In this area, it has been described as Foster's murmur,[9] or the "axillary diastolic murmur in aortic insufficiency."[10] The Flint murmur is a presystolic rumble which practically merges with the first heart sound, and it is limited to a small area at the apex, whereas the directly propagated diastolic murmur is more often heard at a higher level, out in the axilla. They differ sufficiently in most instances to

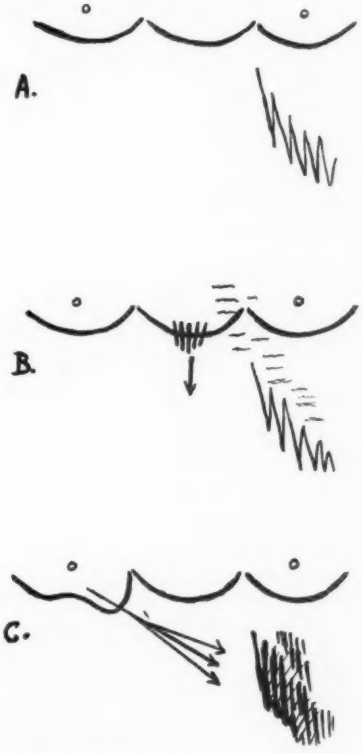


Fig. 5.—Schematic drawing showing (*A*) normal aortic valve and normal anterior mitral curtain; (*B*) perforation at the base of the posterior aortic leaflet, giving rise to vibrations (wave marks) in the aortic ring which are transmitted to the anterior mitral curtain as in the experimental aortic insufficiency of Herrmann. The anterior mitral curtain remains normal. (*C*) Sagging of the right anterior leaflet, especially inner corner (lesion of the Flint murmur), with grooving or diversion of regurgitant stream against the anterior mitral curtain, causing frictional sclerosis of the latter.

permit identification. They may be heard in the same patient.[10] Differentiation of the Flint murmur from presystolic apical gallop rhythm is apparently more difficult. Some clinicians consider the Flint murmur as nothing more than a form of presystolic gallop due primarily to the existence of a large atonic left ventricle.[11, 12] We regard such a hypothesis as singularly ill-founded.

SUMMARY

In a series of ten patients who had Flint murmurs incidental to aortic regurgitation, a characteristic deformity of the right aortic leaflet was found at necropsy. This consisted of a concave, cup-shaped deficiency of the inner portion of the leaflet, so situated as to divert or "groove" the regurgitating blood toward the lower portion of the anterior mitral curtain. The latter exhibited on its ventricular aspect a variable degree of endocardial thickening which was interpreted as a frictional sclerosis.

The posterior aortic leaflet was normal in some cases, and in others was involved in a manner which we believe was insignificant. We do not attempt, on the basis of this small series of patients, to exclude posterior leaflet lesions as occasional factors of importance. Our experience indicates, however, that they are uncommon.

The pathologic changes support the original belief of Austin Flint that a functional mitral stenosis, brought about by aortic regurgitation, is the cause of the presystolic apical murmur bearing his name.

The author is indebted to the medical and laboratory staffs of the Philadelphia General Hospital for the privilege of reporting these cases.

REFERENCES

1. Bellet, S., Gouley, B. A., Nichols, C. F., and McMillan, T. M.: Loud Musical Diastolic Murmurs of Aortic Insufficiency, Am. Heart J. **18**: 483, 1939.
2. Flint, A.: On Cardiac Murmurs, Am. J. M. Sc. **44**: 29, 1862.
3. Guiteras, J.: (a) Three Cases of Acute Endocarditis; Evidences of Dynamic Mitral Stenosis, Med. News **47**: 533, 1885.
   (b) Direct Functional Murmurs, Trans. Ass. Am. Physicians **2**: 37, 1887.
4. Da Costa, J. C.: Physical Diagnosis, Philadelphia, 1913, Ed. 1, p. 310, W. B. Saunders Co.
5. Broadbent, J. F. H.: Heart Disease, London, 1900, Ed. 3, p. 151, Bailliere, Tindall and Cox.
6. Herrmann, G. R.: The Austin Flint Phenomenon, Am. Heart J. **1**: 671, 1926.
7. Sansom, A. E.: Diseases of the Heart and Thoracic Aorta, London, 1892, p. 381, Chas. Griffin and Co.
8. Easby, M. H.: Med. and Surg. Yearbook, Physicians Hospital, Plattsburgh, N. Y., **1**: 90, 1929.
9. Foster, B.: Clinical Medicine, London, 1874, p. 121, J. and A. Churchill.
10. Cole, R., and Cecil, A. B.: The Axillary Diastolic Murmur in Aortic Insufficiency, Johns Hopkins Hospital Bull. **19**: 353, 1908.
11. Pezzi, C.: The Pathogenesis of the Flint Murmur, Arch. Mal. du coeur **9**: 290, 1916.
12. Cuatrecasas, J., and Duclos, F.: Contribution to the Mechanism of Flint's Murmur, Rev. Med. de Barcelona **17**: 195, 1932.

# PAROXYSMAL VENTRICULAR TACHYCARDIA

## Its Favorable Prognosis in the Absence of Acute Cardiac Damage, and Its Treatment With Parenterally Administered Quinine Dihydrochloride

Joseph E. F. Riseman, M.D., and Harry Linenthal, M.D.
Boston, Mass.

PAROXYSMAL ventricular tachycardia is generally regarded as an ominous condition, largely because it occurs as a complication of acute myocardial infarction. The following case reports emphasize that even very severe attacks of ventricular tachycardia, when not associated with acute cardiac damage, may be followed by complete recovery. The purpose of this communication is also to emphasize the fact that quinidine is useful in this condition. In one of the cases, effective treatment by means of parenteral injections of quinine is illustrated.

### REPORT OF CASES

Case 1.—Mr. D. H., 60 years old, had, for a period of 20 years, noticed slight substernal oppression on exertion. A routine physical examination at the time this symptom began revealed an apical systolic murmur; an electrocardiogram seven years later showed prolonged QRS complexes, inverted T waves, and slightly depressed S-T segments in Leads II and III (Fig. 1*A*).

About twenty years after the onset of cardiac symptoms, the patient had attacks of dizziness, associated with palpitation and irregular heart action, which lasted a few seconds to several minutes. Physical examination was negative except for slight cardiac enlargement and a soft blowing systolic murmur at the apex. The blood pressure was 120/80. The electrocardiogram (Fig. 1*B*) was essentially the same as it had been thirteen years previously. The precordial lead showed a positive initial deflection of the QRS complex, with moderate depression of the S-T segment and a negative T wave. The morning after the electrocardiogram was taken, he suddenly experienced marked, irregular palpitation, severe substernal pain radiating down the left arm, dizziness, and faintness. His color was ashen, and he perspired profusely. Sedatives and large doses of quinidine were administered, after which he vomited repeatedly. This first attack lasted several hours. During the following week, while in bed, he experienced numerous similar, but milder, attacks, each initiated by extrasystoles, palpitation, and an increase in the pulse rate from 80 to 150. The heartbeat during some attacks was grossly irregular, with a marked pulse deficit; during other attacks the heartbeat was regular, with occasional accentuation of the first or second heart sounds. Carotid sinus pressure exerted no influence on the cardiac rate or rhythm. Electrocardiograms during the attacks showed periods of irregularity caused by premature beats of ventricular origin, or long periods of ventricular tachycardia (Fig. 1*C*). After the attacks subsided, the electrocardiograms showed only slight differences, as compared with the original tracing of thirteen years previously (Fig. 1*D*).

From the Medical Service and Medical Research Laboratories of the Beth Israel Hospital, and the Departments of Medicine of Harvard Medical School and Tufts Medical School, Boston, Massachusetts.

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When the ventricular rate rose above 150 the patient suffered severe substernal pressure, with pain radiating down the left arm. Quinidine in an amount sufficient to cause nausea and anorexia slowed the rate to 120 or 130 and relieved the pain. A maintenance dose of 3 grains every four hours was administered day and night. During the attacks of ventricular tachycardia 3 grains of quinidine every hour were required to maintain the lower ventricular rates. The largest amount administered in any one day was 42 grains. Constant medical supervision was required, and it is believed that myocardial damage was obviated in large measure by this regime.

These attacks of tachycardia decreased in frequency and severity, and disappeared entirely after seventeen days. Throughout a three-week period of observation he showed no evidence of myocardial infarction. The blood pressure remained at 120/80. There was never any elevation of temperature. The leucocyte count was 8,500. The corrected sedimentation index varied from 0.42 to 0.60. The electrocardiogram between and after attacks showed the original characteristics.

*Subsequent Course.*—In the four years which have elapsed since the above attack, the patient has had two additional attacks. One occurred eleven months later, while he was overexerting himself during a snowstorm, and lasted three hours, during which time he vomited frequently. The third attack, nine months later (Fig. 1*F*), lasted fifteen hours, during which time he received 6 grains of quinidine sulfate every two hours. Vomiting again made it difficult to ascertain how much of this quinidine was absorbed. In none of these attacks was there any change in electrocardiogram, blood cell count, or sedimentation rate to indicate cardiac damage, either as a cause or result of the ventricular tachycardia (Fig. 1*G*).

Since his last attack over two years ago, the patient has been taking 5 grains of quinidine sulfate twice daily. He has led an active, normal life, and does not have as much discomfort on walking as formerly.

## COMMENT

The recent work of Blumgart, Schlesinger, and Davis[1] demonstrates that acute coronary occlusion may produce temporary anoxemia without myocardial infarction and with complete recovery if the collateral circulation is adequate. These authors have also shown that collateral circulation is formed as a response to the demands of the myocardium. It would seem likely, therefore, that the constant creation of such a demand by reasonable activity within the limits of the coronary circulation may be desirable to promote the formation of a collateral circulation. It is possible that the normal, active life of this patient during his twenty years of angina pectoris might have favored the formation of a coronary collateral circulation, and made him withstand the later attacks of ventricular tachycardia without any myocardial damage.

The difficulty in evaluating the effectiveness of quinidine sulfate in the presence of poor absorption from the gastrointestinal tract because of recurrent vomiting and circulatory collapse suggests the need of a soluble preparation of quinidine for parenteral administration. The following case illustrates again the inadequacy, at times, of the oral administration of quinidine sulfate, and indicates the value of intramuscular administration of quinine dihydrochloride under such conditions.

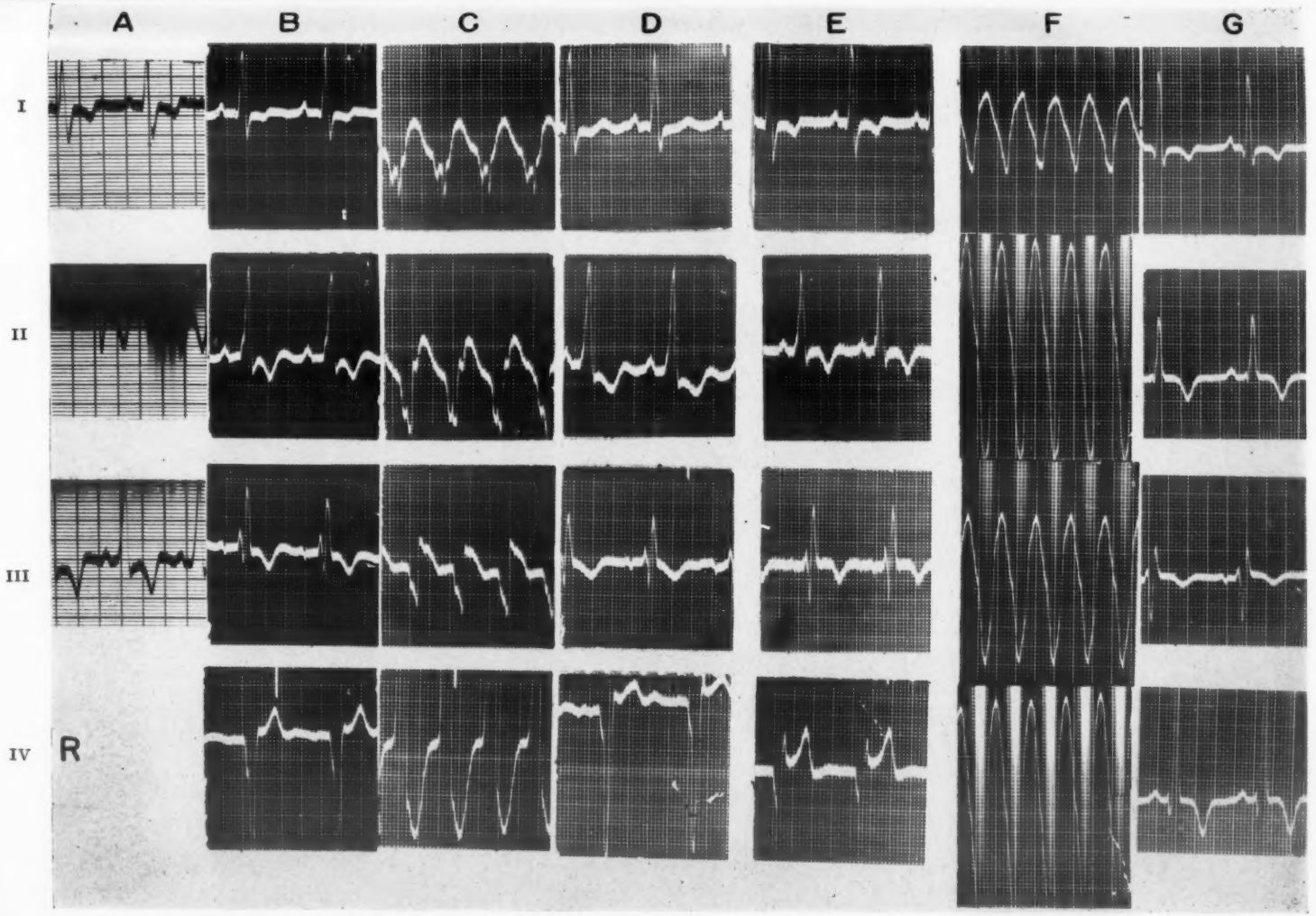


Fig. 1.—Electrocardiogram in Case 1 (D. H.): *A*, July 5, 1924, thirteen years before the first attack of ventricular tachycardia; *B*, Feb. 8, 1937, shortly after the onset of the first attacks of cardiac irregularity (Lead IV R, old method); *C*, Feb. 12, 1937, during an attack of ventricular tachycardia; *D*, Feb. 18, 1937, after recovery from repeated attacks of ventricular tachycardia; *E*, May 8, 1937, after two and one-half months of freedom from tachycardia; *F*, Sept. 2, 1938, during the third attack of ventricular tachycardia; *G*, Sept. 6, 1938, three days after cessation of the last attack (Lead IV R, new method).

CASE 2.—Mr. S. D., a German refugee, aged 54, was well until an attack of myocardial infarction in August, 1937. The attack was followed by transient aphasia, hemiplegia, and mesenteric embolism, and rest in bed for three months was required. The harrowing financial and nervous strain incident to establishing himself in this country prevented him from obtaining the physical and mental rest that his illness necessitated, but nevertheless he felt fairly well.

On Oct. 10, 1939, he suddenly felt faint, and noted that his heart was irregular. Physical examination showed nothing except frequent extrasystoles without compensatory pauses. The blood pressure was 140/80. The electrocardiogram (Fig. 2*A*) showed auricular extrasystoles, both singly and in groups, left-axis deviation, notched QRS waves in Leads III and IV, flat T waves in Leads I and II, and a negative, monophasic QRS in Lead IVR. Each premature auricular beat was followed by a prolongation of the P-R interval.

Quinidine sulfate, 5 grains four times a day, was prescribed. The patient remained in bed for three days, the arrhythmia and faintness subsided, and he felt perfectly well.

On Oct. 16, at 11:00 A.M., while shaving, he suddenly experienced rapid, regular beating of his heart, accompanied by a sense of weakness and faintness. When seen early in the afternoon, he was in bed and fairly comfortable except for the palpitation and slight substernal oppression. His expression was anxious, but he was mentally clear. There were definite pallor and moderate perspiration. The heart was not enlarged, the rhythm was normal, and the rate was 210, with no pulse deficit. The sounds were of good quality but not of uniform intensity, for at times either the first or second sound was accentuated. The blood pressure was 96/60. The lungs were normal, the liver was not enlarged, and there was no peripheral edema. Carotid sinus pressure did not influence the rate or rhythm. A diagnosis of ventricular tachycardia was made, and was confirmed by electrocardiogram (Fig. 2*B*). During the course of the examination he complained several times that everything became "dark," and that he felt as if he were "about to die." At these times the pulse could not be felt, the heart sounds were inaudible, and he became pale and lost consciousness for a few seconds.

Hospitalization was refused, and it was necessary to carry out treatment at home (Fig. 3). Approximately three hours after the onset of the attack, he was given ⅛ grain of morphine sulfate hypodermically, followed by 10 grains of quinidine sulfate every hour for three doses. After the second dose of quinidine the patient vomited a large amount of undigested food, and it was obvious that the quinidine could not have passed through this mass into the intestine. The third dose of quinidine was vomited in tablet form. It was evident that the oral administration of drugs was of little value. About seven hours after the onset of the attack, therefore, quinine dihydrochloride, in a dose of 7½ grains in 5 c.c. solution, was given intravenously. Approximately one minute later marked tinnitus occurred, followed suddenly by another period of unconsciousness. Within fifteen minutes the ventricular rate dropped temporarily to 155, but the electrocardiogram was unchanged. Further intravenous therapy seemed unsafe; accordingly, quinine dihydrochloride was given intramuscularly in a dose of 7½ grains every hour for five hours.

During the second, third, and fourth days it was again possible to administer quinidine by mouth, despite occasional vomiting. During this period the patient was uncomfortable and weak, and râles appeared at the base of the right lung, but his general condition was satisfactory. It was obvious that quinidine induced cardiac slowing, but it could not be administered orally in doses sufficiently large to reduce the rate to normal. On the fourth day atropine sulfate was administered at two-hour intervals for three doses, beginning with $\frac{1}{150}$ of a grain and increasing each dose so that the third dose was $\frac{1}{50}$ of a grain; this was without any demonstrable effect.

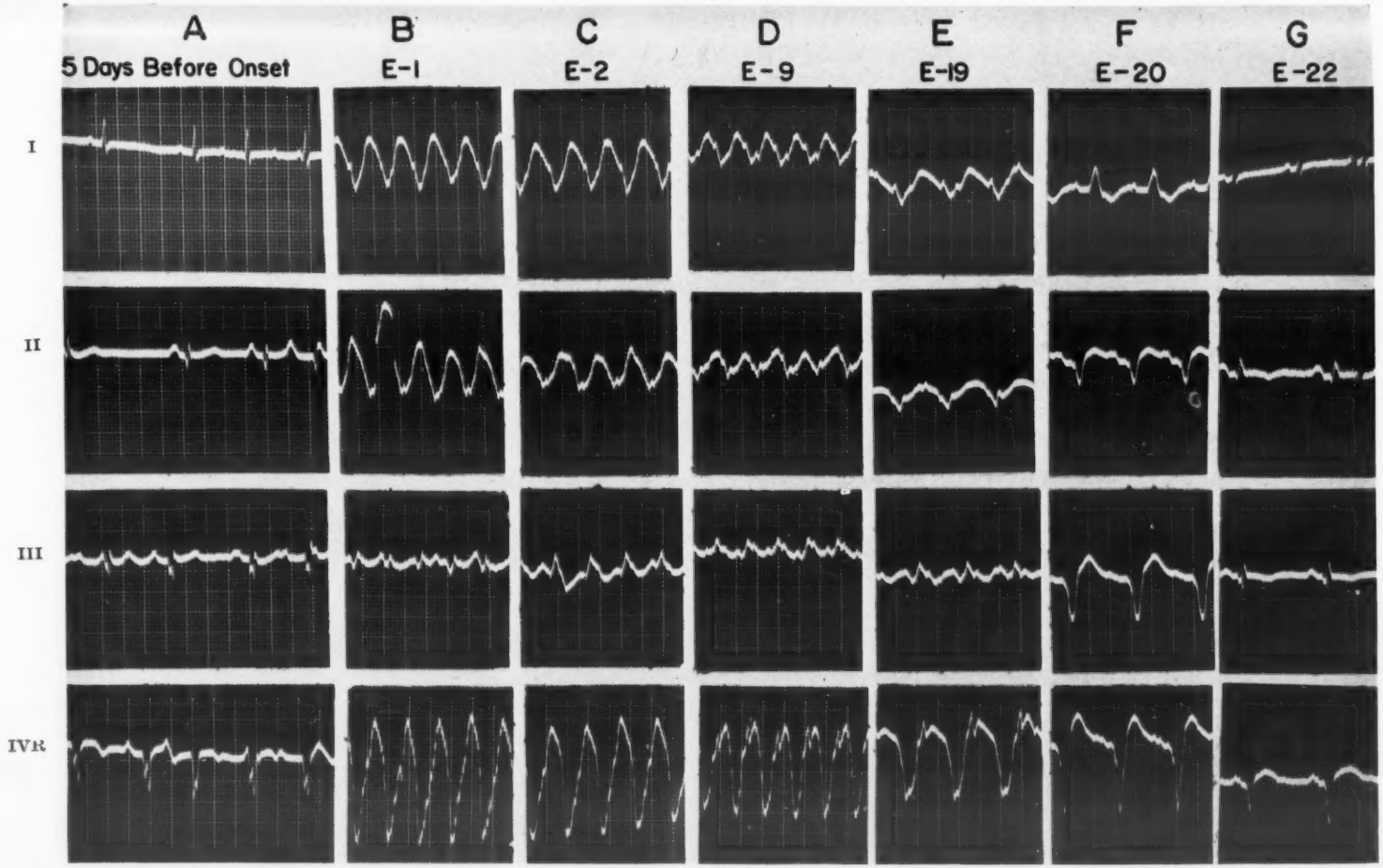


Fig. 2.—Electrocardiogram in Case 2 (S. D.): *A*, Oct. 11, 1939, shortly after the onset of auricular premature beats, five days before the onset of ventricular tachycardia; *B*, Oct. 16, 1939, approximately four hours after the onset of ventricular tachycardia; *C*, one-half hour after the administration of quinine dihydrochloride intravenously; *D*, Oct. 21, 1939, after the administration of 12 grains of digitalis; *E*, Oct. 24, 1939, shortly before the cessation of the attack; *F*, less than one hour after the cessation of the attack; *G*, Oct. 26, 1939, two days after the return to normal rhythm.

During the fifth day quinidine was discontinued because of vomiting. Six hours later his pulse rate began to rise. In ten hours it was again 210, and periods of unconsciousness occurred. The administration of quinidine sulfate was again followed by a fall in heart rate to 160, but the rhythm was not converted to normal. The patient's condition had become worse. There were signs of consolidation at the base of the right lung, and numerous râles at the base of the left. He developed respiratory difficulty, coughed frequently, and raised large amounts of sputum which was occasionally bloodstreaked. He had slight fever, and developed considerable abdominal distention and slight edema of his legs and over his sacrum. Cyanosis was controlled by oxygen therapy.

Digitalis was given in the hope of producing intraventricular block, and for its tonic effect on the failing myocardium. Because of the danger of precipitating ventricular fibrillation, the digitalis was given in doses of 3 grains every four hours, together with a maintenance dose of quinidine (5 grains), and frequent electrocardiograms were taken in order to recognize early any untoward digitalis effect. After the fourth dose of digitalis (on the sixth day), the heart rate again increased; the patient became weak and disoriented, complained of substernal pain, and had a period of unconsciousness during which the heart rate was over 200 and the pulse was imperceptible. The electrocardiogram (Fig. 2*D*) showed a definite decrease in the amplitude of the QRS complexes and a deep notch in Lead IV. Digitalis was discontinued and the dose of quinidine sulfate was again increased, after which the heart rate fell to 170 and the patient's condition improved slightly.

On the seventh day, despite quinidine, the heart rate increased and he had periods of unconsciousness. Quinine dihydrochloride was given intramuscularly again, and approximately one-half hour later his condition improved considerably. The intramuscular administration of quinine dihydrochloride was continued; at first it was given every hour when he was awake, and every 3 to 4 hours when he was asleep; later, every 2 hours, day and night. Each dose was followed by perceptible slowing of the heart.

On the ninth day it was evident that the auricular and ventricular rates were approximately the same, for after accentuation of the heart sounds for several consecutive beats the sounds would be normal in intensity. In the hope of speeding up the auricular rate and possibly decreasing the auriculoventricular block, atropine sulfate was given again in the same way that it had been on the fourth day. Again this had no demonstrable effect on the cardiac rate or rhythm; after the third dose, however, the patient became disoriented and confused. Because of weakness, seven doses of $\frac{1}{30}$ grain of strychnine sulfate were given at intervals of four hours.[2]

At 7:10 P.M. on the ninth day of the illness the heart rate was 124, and the electrocardiographic complexes were of the same character as had been observed previously, except that with the slowing of the rate the duration of the complexes increased (Fig. 1*E*). At 7:45 P.M. the heart rate was 108, the patient was sleeping comfortably, his pulse was full and strong, and his blood pressure was 120/80. The heart sounds were of good quality and of uniform intensity, and the rhythm was normal. The electrocardiogram (Fig. 2*F*) showed sinus rhythm, prolonged A-V conduction time (0.22 second), prolonged QRS complexes (0.12 second), deep S waves in Leads II and III, elevated S-T segments in Leads II, III, and IV, and inversion of the T wave in Lead I.

During the first three days after the termination of the tachycardia the patient was comfortable, but weak; the cough, abdominal distention, and edema disappeared, and the patient complained of his forced inactivity. Roentgenologic examination showed mottling of the lower two-thirds of both lungs, with a moderate degree of atelectasis and a small amount of fluid in the right pleural sac. The erythrocyte count was 4,710,000, the leucocyte count was 19,100, and the differential count was

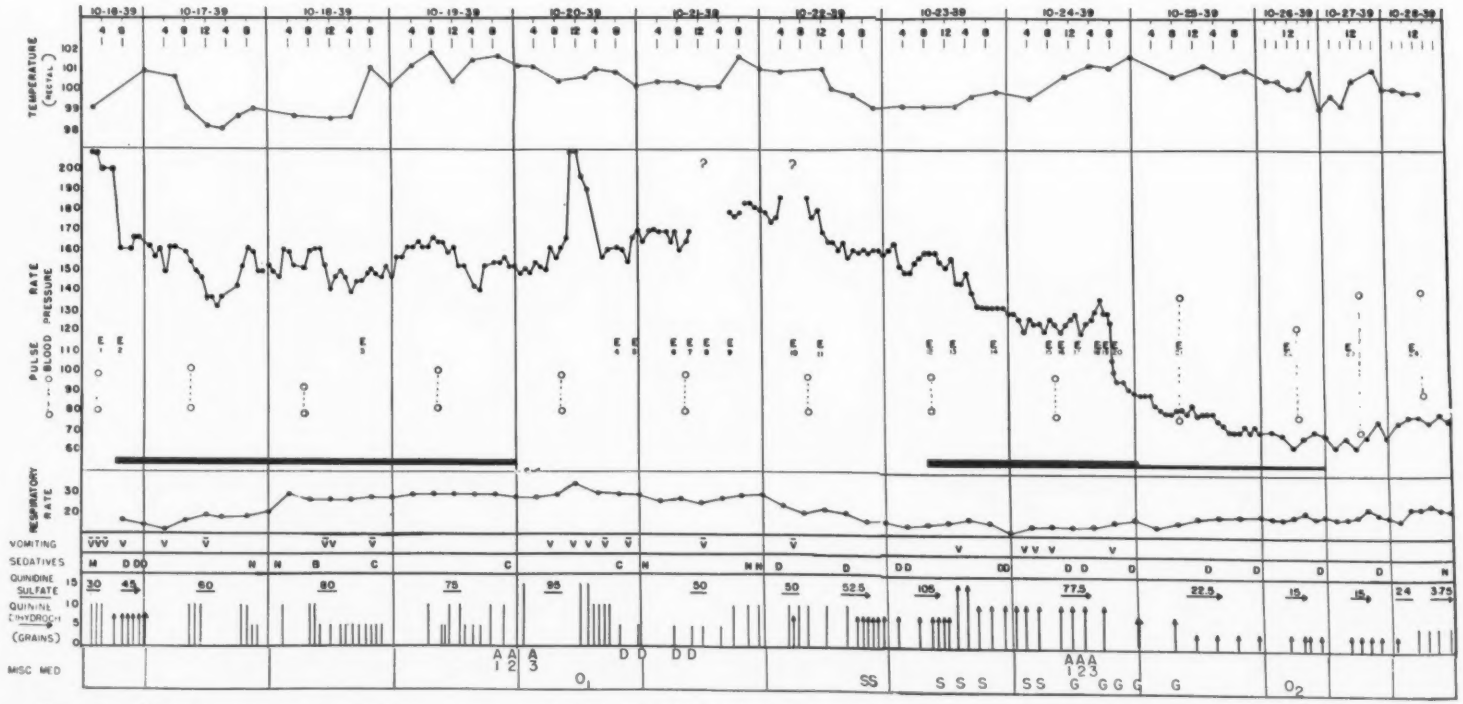


Fig. 3.—Clinical course and treatment in Case 2 (S. D.) *Symbols: E,* Electrocardiogram (numbers refer to Fig. 2). ▬, Tinnitus. *V,* Vomiting. $\overline{V}$, Vomiting caused by medication. *M,* Morphine sulfate, ⅛ grain. *D,* Dilaudid, 1/20 grain. *N,* Nembutal, 1½ grains. *B,* Triple bromides, 15 grains. *C,* Chloral hydrate, 15 grains. —, Quinidine sulfate by mouth. →, Quinine dihydrochloride parenterally (the first injection was given intravenously; all others were given intramuscularly). $A_1$, Atropine sulfate, 1/150 grain; $A_2$, 1/75 grain; $A_3$, 1/50 grain. $O_1$-$O_2$, Duration of intermittent oxygen therapy. *D,* Digitalis, 3 grains. *S,* Strychnine sulfate, 1/30 grain. *G,* Rectal administration of glucose.

normal. The urine examination was negative. The corrected sedimentation index was 0.72. The blood serologic reactions were negative. The patient remained in bed for two weeks, during which time his strength gradually returned. One month after his illness he resumed normal activity. The basal metabolic rate was minus 4 per cent. He has remained active during the two years which have elapsed since this attack.

This conversion of the rhythm to normal on the ninth day after the onset of the tachycardia took place approximately two hours after the last intramuscular injection of quinine dihydrochloride. A total of 240 grains had been given intramuscularly in the forty-eight hours preceding the conversion to normal rhythm. A maintenance dose of 5 grains of quinine was given intramuscularly four times a day for a few days, and then he was given quinidine sulfate by mouth (5 grains every four hours). The tinnitus disappeared forty-eight hours after the cessation of the massive doses of quinine dihydrochloride; the only untoward effect of the drug thereafter was moderate soreness and induration of the buttocks at the points of intramuscular injections.

## DISCUSSION

That paroxysmal ventricular tachycardia may occur in persons without organic heart disease is not generally recognized, although several instances have been reported.[3-6] The two patients presented here had coronary artery disease, but the tachycardia was not precipitated by any evident acute cardiac lesion. Recovery was complete. The duration of the attack in Case 2 was 8½ days. Although attacks of longer duration have been reported,[7] most patients die earlier of cardiac insufficiency unless the paroxysm is ended or the ventricular rate is decreased.

Oppolzer,[8] in 1866, advised small doses of quinine (1 to 2 grains every 2 to 3 hours) for its tonic effect in cases of tachycardia accompanied by a weak pulse. According to available knowledge, quinine and its isomer, quinidine, act on the heart by prolonging the refractory period and the conduction time. The latter effect results in a prolongation of the interval from the beginning of the Q to the end of the T wave (the duration of electrical systole[9]), as demonstrated by the electrocardiograms in Case 2. Frey, in 1918,[10] found that quinidine hydrochloride was more effective than quinine in the treatment of auricular fibrillation. Lewis and his co-workers[11] later estimated that quinidine was five to ten times more effective than quinine in slowing the auricular rate; these authors concluded that all of the alkaloidal salts were of equal value because they were transformed in the stomach to the hydrochloride. It is obvious from the above cases, however, that when the attack is associated with circulatory collapse and vomiting (which frequently occur in acute arrhythmias) absorption from the gastrointestinal tract cannot be depended upon, and under such conditions of emergency an injectable preparation is desirable.

Hepburn and Ryckert[12] have advised the intravenous administration of quinidine sulfate. Since approximately 10 c.c. of saline are required to dissolve one grain of the drug, this method necessitates the intravenous administration of comparatively large volumes of fluid to cardiac

patients. It is impractical for the physician to carry such large volumes for emergency therapy, and, furthermore, the preparation of this solution requires more time than is usually available in such an emergency. The need of a small ampoule for emergency use is obvious. The preparations now available from the American pharmaceutical houses are relatively insoluble, but the more soluble quinine salts may be employed for parenteral use.

The indications for quinine therapy would appear to be: (1) acute arrhythmias or tachycardias, when quinidine would ordinarily be used but cannot be given by mouth because of vomiting or shock; (2) prolonged arrhythmias which are only partially controlled by the oral administration of quinidine sulfate.

The amount of medication necessary to interrupt the abnormal rhythm varies in different persons. In our experience with paroxysmal ventricular tachycardia, the administration of a small test dose is unnecessary, for it results in loss of valuable time, and the danger of collapse or death from continuation of the arrhythmia may be greater than the danger from hypersensitivity to the drug. An initial dose of 10 to 15 grains may be given, and this may be repeated every two, or two and a half, hours. This results in a gradual increase in effect, and, at the same time, permits evaluation of the effect of previous doses before continuing medication. More frequent administration may result in toxic effects after the therapeutic result has been obtained; less frequent administration (every four hours) is impractical because it is too time-consuming and does not result in an increased effect unless the amount given is increased with each dose.

Intramuscular administration is the route of choice. According to available knowledge,[13] the drug is fixed by tissues, including the myocardium, within one-half hour. Renal excretion begins in about one-half hour and becomes minimal in approximately four hours. The effect on the auricular rate begins about one-half hour after oral administration, reaches a maximum in two hours, begins to decrease gradually after three hours, and has ceased almost entirely within twenty-four hours.[11]

Levine[14] has suggested the use of atropine in cases of ventricular tachycardia in which the attack is not controlled by quinidine orally. Carter and Traut[2] have reported that strychnine enhances the effect of quinidine. Neither atropine nor strychnine had any demonstrable beneficial effect in our case.

Levy[15] has listed the untoward effects of quinidine, the majority of which were observed when auricular fibrillation had been converted to normal rhythm. In our experience with over 100 patients with coronary artery disease and normal rhythm (angina pectoris) who received 5 grains of quinidine sulfate four times daily, the only untoward effects observed were diarrhea and, in an occasional instance, urticaria or

slight gastric distress. The increase in ventricular rate which reputedly follows the administration of quinidine was not the rule, and, if it occurred, amounted to less than 10 beats per minute,[16, 17] with these doses.

The possibility of inducing ventricular tachycardia or fibrillation by the administration of quinidine deserves special mention. The literature reports seven instances in which this apparently took place;[15, 18, 19, 20] all except two occurred in cases in which quinidine was being given to abolish auricular fibrillation. In cases of auricular fibrillation the administration of quinidine is followed by a slowing of the auricular rate and an increase in the ventricular rate. Unless digitalis is given simultaneously with the quinidine, the absence of A-V block may result in a response of the ventricle to each auricular stimulus, and, therefore, ventricular tachycardia or fibrillation. In the two cases reported by Schwartz and Jezer,[20] the patients did not have auricular fibrillation, but suffered from frequent attacks of ventricular fibrillation which occurred spontaneously or could be precipitated by several drugs, including quinidine given intravenously. In treating patients with angina pectoris, we have not observed ventricular premature beats or abnormal rhythms as a result of quinidine therapy; indeed, the drug is frequently of value in eliminating premature contractions of the ventricle or auricle.

Prompt treatment of ventricular tachycardia requires prompt diagnosis. Although the electrocardiogram is the most specific diagnostic procedure, Levine and Fulton[21] have pointed out the characteristics which make a clinical diagnosis possible: "First, the rhythm is rapid and essentially regular, but slight irregularities can be detected. Second, the quality of the first heart sound varies in intensity in some of the cycles. Third, attempts at vagal or ocular pressure prove ineffective in slowing the tachycardia." In our experience, the variation in the intensity of the heart sounds is the greatest aid in diagnosis. The lack of response to carotid sinus pressure serves to differentiate tachycardias originating in the ventricles from those originating above the A-V node. We were unable to recognize any irregularity in our two cases, either clinically or with the electrocardiogram.

## SUMMARY

Two cases of paroxysmal ventricular tachycardia which demonstrate that this condition may occur without preceding or subsequent cardiac damage are presented. Under such conditions prompt diagnosis and treatment are essential, and may result in complete functional recovery. The importance of quinidine sulfate in the treatment is illustrated: even when the drug fails to cause conversion to normal rhythm, it may control the ventricular rate and thus prevent prolonged, severe, myocardial anoxemia, cardiac pain, and myocardial damage. In the presence of vomiting or circulatory collapse, poor absorption from the gastro-

intestinal tract makes parenteral therapy advisable; quinine dihydrochloride may be used under such conditions.

We wish to express our appreciation to Dr. Herrman L. Blumgart and Dr. Paul D. White, who saw these patients in consultation, and to the Misses Loretta and Rose Gilmartin for their excellent nursing care of patient S. D. under trying conditions.

## REFERENCES

1. Blumgart, H. L., Schlesinger, M. J., and Davis, D.: Studies of the Relation of the Clinical Manifestations of Angina Pectoris, Coronary Thrombosis, and Myocardial Infarction to the Pathologic Findings, AM. HEART J. **19**: 1, 1940.
2. Carter, J. B., and Traut, E. F.: Quinidine and Strychnine in the Treatment of Premature Contractions, Am. J. M. Sc. **189**: 206, 1935.
3. Andersen, M. C.: Paroxysmal Ventricular Tachycardia, Am. J. M. Sc. **181**: 309, 1931.
4. Scott, R. W.: Observations on a Case of Ventricular Tachycardia With Retrograde Conduction, Heart **9**: 297, 1922.
5. Strauss, M. B.: Paroxysmal Ventricular Tachycardia, Am. J. M. Sc. **179**: 337, 1930.
6. Wilson, F. H., Wishart, S. W., Macleod, A. G., and Barker, P. S.: A Clinical Type of Paroxysmal Tachycardia of Ventricular Origin in Which Paroxysms Are Induced by Exertion, AM. HEART J. **8**: 155, 1932.
7. Willins, F. A.: Paroxysmal Tachycardia of Ventricular Origin, Boston M. and S. J. **178**: 40, 1918.
8. Oppolzer: Vorlesungen über die Krankheiten des Herzens und der Gerfässe, edited by E. R. von Stoffella. Erlangen, 1866.
9. Landau, N.: Über die Verlangerung der Systole bei Tetanie und ihre Beeinflussung durch verschiedene Pharmaca, Klin. Wchnschr. **17**: 93, 1938.
10. Frey, W.: Ueber Vorhofflimmern beim Menschen und seine Beseitigung durch Chinidin, Berlin klin. Wchnschr. **55**: 450, 1918.
11. Lewis, T., Drury, A. N., Wedd, A. M., and Iliescu, C. C.: Observations Upon the Action of Certain Drugs Upon Fibrillation of the Auricles, Heart **9**: 207, 1922.
12. Hepburn, J., and Rykert, H.: The Use of Quinidine Sulfate Intravenously in Ventricular Tachycardia, AM. HEART J. **14**: 620, 1937.
13. Weisman, S. A.: Further Studies in the Use of Quinidine in the Treatment of Cardiac Irregularities, Minnesota Med. **22**: 385, 1939.
14. Levine, S. A.: Clinical Heart Disease, Philadelphia, 1940, W. B. Saunders.
15. Levy, R. L.: The Clinical Toxicology of Quinidine, J. A. M. A. **78**: 1919, 1922.
16. Riseman, J. E. F., and Brown, M. G.: Medicinal Treatment of Angina Pectoris, Arch. Int. Med. **60**: 100, 1937.
17. Freedberg, A. S., Riseman, J. E. F., and Spiegl, E. D.: Objective Evidence of the Efficacy of Medicinal Therapy in Angina Pectoris. AM. HEART J. In press.
18. Davis, D., and Sprague, H. B.: Ventricular Fibrillation: Its Relation to Heart Block, AM. HEART J. **4**: 559, 1929.
19. Kerr, W. J., and Bender, W. L.: Paroxysmal Ventricular Fibrillation With Cardiac Recovery in a Case of Auricular Fibrillation and Complete Heart Block While Under Quinidine Sulfate Therapy, Heart **9**: 269, 1922.
20. Schwartz, S. P., and Jezer, A.: The Action of Quinine and Quinidine on Patients With Transient Ventricular Fibrillation, AM. HEART J. **9**: 792, 1934.
21. Levine, S. A., and Fulton, M. N.: The Effect of Quinidine Sulphate on Ventricular Tachycardia, J. A. M. A. **92**: 1162, 1929.

# A QUANTITATIVE ELECTROCARDIOGRAPHIC STUDY OF DIGITALIZATION

ARTHUR J. GEIGER, M.D., LOREN F. BLANEY, M.D., AND
WILLIAM H. DRUCKEMILLER, M.D.
NEW HAVEN, CONN.

THERE appears to be a widespread impression that the electrocardiogram offers a method for quantitative estimation of the degree to which a patient is digitalized, and that such a record is a valuable aid in therapy. General statements to this effect are often made or implied in textbook discussions of digitals and the electrocardiogram. We have always felt reluctant to place such reliance on electrocardiographic features. It is, of course, acknowledged that a tracing may show certain changes in the RS-T segment and T wave which are so commonly associated with the administration of digitalis that the experienced observer immediately recognizes the abnormality as a characteristic effect of the drug. Moreover, the electrocardiogram may admittedly give valuable and sometimes almost certain evidence of *toxic* digitalis action. Our purpose, however, was primarily to learn whether any reasonably reliable and useful *quantitative* relationships exists with respect to electrocardiographic changes accompanying the *clinical* use of the drug in *therapeutic* doses.

A search of the literature has disclosed relatively few clinical studies bearing directly on this subject. One of the earliest electrocardiographic studies of digitalization in man was reported in 1915 by Cohn, Fraser, and Jamieson.[1] These observers clearly established that digitalis either lowered or inverted the T wave and depressed the RS-T segment in the majority of the tracings of the thirty-four patients whom they studied. Although some of the subjects were admittedly intoxicated by the doses of digitalis which were administered, nevertheless definite electrocardiographic changes apparently resulted from exhibition of the drug in therapeutic amounts, also. No attempt was made in this work to correlate the nature or extent of the changes in RS-T and T with degrees of clinical digitalization. Shortly after the report by Cohn and his collaborators, White and Sattler[2] described lowering of the T wave as an early effect of digitalis, and Pardee[3] attempted to apply this phenomenon in the assay of digitalis preparations, but a lack of uniformity in the electrocardiographic effects of the drug was evident, even though the number of cases was small.

From the Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut.
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Larsen, Neukirch, and Nielsen[4] reviewed the literature of this subject up to 1937, and described their own studies of the electrocardiographic changes which occurred in 15 normal adults after digitalis administration. As the subject has changed but little since then, a summary of their review may serve to indicate the present status of the problem. The consensus was that the P-R (or P-Q) intervals showed inconstant increases in duration, sometimes to the point of partial A-V block; but these changes could not be correlated with definite therapeutic states of digitalization. Only infrequent and relatively slight changes in the RS-T segment were observed, and these consisted usually of slight depression of the RS-T segment, or slight diminution in the height of the T wave. Concerning the T wave, Larsen and his associates commented, "Although the statements in the literature concerning the effect of digitalis administration on the shape of the T wave in normal subjects on the whole are in good agreement, all possible variations have been reported."

Stewart and Watson,[5] in a recent study directed particularly toward the effect of digitalis on the form of the chest-lead electrocardiogram, illustrated eight representative types of electrocardiographic changes following digitalis. In only one of the series of tracings depicted (Stewart and Watson's figure 5), was either the RS-T segment notably depressed or the direction of T reversed in the conventional limb leads; on the other hand, a variable diminution in the amplitude of the T wave was noted in one or more leads of the other series of tracings shown. More recently, Levy and Boas,[6] in comparing the electrocardiographic effects of gitalin and digitalis in thirty-five cases, stated that the two drugs gave similar results. In 11 cases neither drug in therapeutic doses produced changes in the T wave, whereas both drugs produced only slight alterations in T in twelve cases, moderate changes in ten, and marked effects in only two.

Although there is general uniformity of opinion that digitalis tends chiefly to depress the RS-T segment and diminish the amplitude of, or invert, the T wave, no direct correlation has apparently been established between the doses of digitalis which were administered and the resultant changes in RS-T and T, and there appears to be no reliable evidence from previous experimental work that the electrocardiogram can serve as a measure of the degree of digitalization of a patient.

The few reported studies of the Q-T duration all agree that digitalis effects a relative shortening of this interval. Cheer and Dieuaide[7] considered that such a shortening of the Q-T interval was a more sensitive indicator of digitalis effect than lengthening of P-R, and a more definite change than alterations in the T wave.

Inasmuch as most of the leading reports concerning digitalis effects on the electrocardiogram antedated the general use of precordial leads, there has been relatively little written about this particular aspect

since the report by Strauss and Katz[8] that digitalis may cause inversion of the T wave in the chest lead. In a thorough study of the subject in thirty cases, Stewart and Watson[5] found that digitalis in therapeutic amounts resulted in some alteration of the T wave (which became lower in amplitude or reversed in direction) in all but one instance; changes in the RS-T segment were encountered in only a third of the cases, and were considered less marked than changes in the T wave. No attempt was made to relate the nature or degree of RS-T and T-wave changes to specific amounts of digitalis, and no correlation seemed evident, for various degrees of change, from none to considerable, were encountered in different cases in which similar amounts of digitalis were given. Casual observation of electrocardiograms taken routinely in this laboratory has abundantly demonstrated that digitalis may alter the RS-T segment level and T wave in the precordial lead, and has also confirmed the observation of Stewart and Watson[5] that the degree of change suffered by T in the precordial lead is frequently more pronounced than in the limb leads.

It appeared, from these various reports, at least, that no definite quantitative relationship had been clearly established between digitalis concentrations and electrocardiographic changes. However, it seemed to us that the subject had been inadequately explored, and that further study was required, not only of the effects on normal subjects, but more particularly on patients with heart disease in various functional states. Moreover, it seemed promising to study more thoroughly the shortening of the Q-T interval which was attributed to digitalis by Cheer and Dieuaide;[7] and, finally, it was considered interesting to learn whether precordial leads offer any advantage over the conventional limb leads in the quantitative estimation of digitalization.

## SECTION I

### A STUDY OF PROGRESSIVE DIGITALIZATION IN TEN NORMAL SUBJECTS

Ten normal male volunteers, ranging in age from 22 to 32 years, were studied electrocardiographically during progressive digitalization. None of the subjects had a history or physical signs of heart disease; roentgenograms of the chest showed hearts of normal configuration and size, and all had normal blood pressures.

Consistency in procedure was sought by administering the digitalis in a predetermined and uniform manner. Each subject received a total dose of digitalis, U.S.P. (Davies, Rose, and Company), which was calculated on the basis of 0.1 Gm. per 10 pounds of body weight, *plus* 0.15 Gm. for each day of the digitalizing period to compensate adequately for excretion. Since the digitalis employed met the U.S.P. XI assay requirements, the total quantity of the drug administered was approximately 30 per cent *in excess* of the theoretically optimal digitalizing dose.[9] One-third of the total dose was given on the initial day, and the remaining two-thirds was administered in equal portions during the following four days.

Electrocardiograms, including the three conventional limb leads and precordial lead IV F,[10] were recorded four hours after each dose, and several follow-up tracings were obtained at weekly intervals for one month longer, or until the electrocardio-

gram was identical with the original record. Electrocardiographic measurements included the P-R interval, Q-T duration (considered in relation to R-R time), changes in the RS-T segment, and alterations in the amplitude and direction of the T wave. Although these features were studied in all leads, it was found that Lead II was fully representative of the limb leads with regard to the P-R and Q-T measurements, and therefore, for reasons of simplicity, these particular data are presented in Table I for Leads II and IV F only. The T-wave amplitude and direction (see Table II) were studied in all four leads. The values indicated in Tables I and II represent average measurements of at least three successive complexes or waves.

TABLE I

ELECTROCARDIOGRAPHIC CHANGES FOLLOWING DIGITALIZATION OF NORMAL ADULT MALES

| PATIENT NO. | DIGITALIS PER CENT | LEAD II | | | | LEAD IV F | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | P-R SEC. | Q-T* SEC. | R-R* SEC. | "K" | P-R SEC. | Q-T SEC. | R-R SEC. | "K" |
| 1 | 0 | .18 | .386 | .766 | .411 | .16 | .360 | .733 | .421 |
| | 130 | .20 | .333 | .933 | .346 | ? | .337 | .960 | .345 |
| 2 | 0 | .17 | .340 | .713 | .403 | .16 | .346 | .740 | .403 |
| | 130 | .16 | .380 | 1.233 | .343 | .17 | .366 | 1.153 | .342 |
| 3 | 0 | .16 | .393 | .980 | .397 | ? | .400 | 1.007 | .394 |
| | 130 | .18 | .340 | 1.160 | .317 | ? | .367 | 1.253 | .327 |
| 4 | 0 | .18 | .373 | .993 | .373 | .16 | .380 | .993 | .382 |
| | 130 | .17 | .366 | 1.033 | .365 | .16 | .353 | .926 | .367 |
| 5 | 0 | .16 | .375 | 1.000 | .375 | ? | .376 | 1.060 | 3.69 |
| | 130 | .16 | .340 | .750 | .393 | .16 | .326 | .800 | .365 |
| 6 | 0 | .16 | .360 | .833 | .394 | .16 | .420 | .926 | .436 |
| | 130 | .16 | .346 | .713 | .410 | ? | .393 | 1.000 | .393 |
| 7 | 0 | .14 | .340 | .700 | .408 | .16 | .340 | .680 | .412 |
| | 130 | .18 | .360 | .920 | .376 | .18 | .346 | .913 | .363 |
| 8 | 0 | .17 | .393 | .753 | .454 | .16 | .360 | .820 | .397 |
| | 130 | .18 | .360 | .726 | .423 | .18 | .353 | .753 | .403 |
| 9 | 0 | .16 | .373 | .806 | .416 | .14 | .360 | .800 | .403 |
| | 130 | .15 | .360 | .860 | .388 | .15 | .353 | .820 | .386 |
| 10 | 0 | .18 | .367 | .780 | .415 | .14 | .327 | .840 | .357 |
| | 130 | .20 | .393 | 1.060 | .381 | ? | .330 | 1.033 | .320 |

*Values represent averages of 3 to 5 measurements.

## RESULTS

As may be seen from Table I, the P-R duration increased not more than 0.02 second in about half the records, whereas the remainder showed no change or very slight shortening. These alterations were probably within the limits of expected variation for the changes in heart rate. The P wave was usually either absent or poorly defined in Lead IV F, and P-R intervals were not satisfactorily measurable. It was apparent that a change in the P-R duration could not serve as a quantitative measure of digitalization, even when moderately excessive doses of the drug had been administered.

2. The Q-T time was considered in relation to the cardiac cycle length, following the method of Cheer and Dieuaide,[7] who employed a modification of Bazett's formula, as follows:

Q-T = "K" times the square root of R-R;

or

"K" = Q-T divided by the square root of R-R.

"K" has been found to be relatively constant within narrow limits when the heart is normal,[11] and increased when it is failing.[7] It is evident from the equations that a decrease in Q-T, relative to R-R, will result in a smaller value for "K." Although Table I indicates that "K" was diminished in eight of the ten subjects at the height of digitalization, careful analysis of the intermediate electrocardiograms revealed that this change was not a progressive one; in fact, the values for "K" in the successive records of the majority of the subjects showed considerable irregular variation, and the seemingly consistent effects in Table I are probably quite fortuitous.

3. In a majority (60 per cent) of the normal records the RS-T segment was very slightly (less than one millimeter) above the isoelectric line, and was lowered to the isoelectric line during the administration of digitalis. In about half the records the RS-T segment was less than one millimeter below the isoelectric line at the height of the digitalis effect. These changes were not only regarded as within the limits of normal variation, but they were entirely too slight to serve as a quantitative measure of digitalization.

4. The T-wave changes during progressive digitalization were remarkable chiefly for their inconsistency in character and their relatively small magnitude. As may be seen from Table II, slight inversion of T developed only three times among the forty leads from the ten subjects, and T became diphasic only three times. A reduction in the amplitude of T was a common accompaniment of digitalization, and this was most pronounced in the precordial lead. But in only three of the subjects (Nos. 2, 8, and 10) was this a uniformly progressive effect with increasing digitalization; in all the remainder the T wave gained positive amplitude in one or more leads at either the theoretically optimal level of digitalization, as compared with the normal, or at the overdigitalization level, as compared with the optimal (note especially subject No. 4 in Table II). This result came as a distinct surprise. One is led to surmise that physiologic variations, as well as digitalis influence, must account for such alterations in the character of the T wave.

The indefinite effects of digitalis on the RS-T segments and T waves in each lead of the records from the normal subjects are graphically depicted in Figs. 2 and 3.

It is apparent from the above that the electrocardiographic changes which accompanied progressive digitalization of these normal subjects

TABLE II

T-WAVE CHANGES FOLLOWING DIGITALIZATION OF NORMAL ADULT MALES

| PATIENT NO. | DIGITALIS PER CENT | T WAVES (MM.) | | | |
|---|---|---|---|---|---|
| | | I* | II | III | IV F |
| 1 | 0 | +2.0 | +4.0 | +2.5 | +4.5 |
| | 100 | +2.5 | +4.0 | +1.5 | +5.0 |
| | 130 | +2.5 | +2.5 | ±1.5 | +5.5 |
| 2 | 0 | +2.0 | +2.5 | ±0.5 | +4.5 |
| | 100 | +1.0 | +1.5 | +0.5 | +1.0 |
| | 130 | +1.0 | +1.0 | +0.5 | +1.5 |
| 3 | 0 | +3.0 | +7.0 | +3.5 | +7.0 |
| | 100 | +1.5 | +3.5 | +3.0 | +5.0 |
| | 130 | +1.5 | +6.5 | +3.0 | +6.0 |
| 4 | 0 | +3.5 | +4.5 | +1.0 | +8.0 |
| | 100 | +1.5 | +2.0 | -1.0 | +2.0 |
| | 130 | +5.0 | +4.5 | ±1.5 | +5.0 |
| 5 | 0 | +5.0 | +4.5 | -1.0 | +6.5 |
| | 100 | +2.5 | +2.5 | ±1.0 | ±1.5 |
| | 130 | +2.5 | +2.5 | ±1.0 | +4.0 |
| 6 | 0 | +3.0 | +3.0 | +1.5 | +5.0 |
| | 100 | +2.0 | +2.0 | ±1.0 | +1.0 |
| | 130 | +2.0 | +2.0 | 0.0 | +2.5 |
| 7 | 0 | +2.0 | +4.0 | +2.5 | +6.0 |
| | 100 | +2.0 | +2.5 | +1.0 | +3.0 |
| | 130 | +2.0 | +3.0 | +1.0 | +1.5 |
| 8 | 0 | +3.0 | +6.0 | +3.5 | +9.0 |
| | 100 | +3.0 | +4.0 | +1.5 | +6.0 |
| | 130 | +3.0 | +4.0 | +1.5 | +6.0 |
| 9 | 0 | +2.0 | +2.0 | +0.5 | +3.5 |
| | 100 | +3.0 | +2.0 | -1.0 | +6.0 |
| | 130 | +1.5 | +1.5 | ±0.5 | +2.5 |
| 10 | 0 | +3.0 | +3.5 | +0.5 | +3.0 |
| | 100 | +2.0 | +1.5 | -1.0 | +2.0 |
| | 130 | +1.0 | +1.5 | ±1.0 | +1.5 |

*Numerals refer to leads.

were too small in degree and too inconstant in character to indicate any quantitative correlation between the electrocardiographic effects and corresponding degrees of digitalization. This was true even when digitalis was administered in a dose which was presumably in the early toxic range.

## SECTION II

### A STUDY OF PROGRESSIVE DIGITALIZATION OF TEN PATIENTS WITH HEART DISEASE AND CONGESTIVE FAILURE

The possibility that patients with diseased hearts might show digitalis effects different in kind and in degree from those observed in the preceding experiments on normal subjects led us to study in similar fashion ten patients with congestive failure caused by heart disease of various kinds. All of these subjects were hospitalized; their ages ranged from

TABLE III

ELECTROCARDIOGRAPHIC CHANGES FOLLOWING DIGITALIZATION OF PATIENTS WITH CONGESTIVE FAILURE

| PATIENT NO. | DIGITALIS PER CENT | LEAD II | | | | LEAD IV F | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | P-R SEC. | Q-T* SEC. | R-R* SEC. | "K" | P-R SEC. | Q-T SEC. | R-R SEC. | "K" |
| 11 | 0 | 0.20 | 0.353 | 0.753 | 0.407 | ? | unreadable | | |
| | 130 | 0.20 | 0.333 | 0.827 | 0.367 | 0.16 | 0.320 | 0.806 | 0.352 |
| 12 | 0 | ? | 0.373 | 0.653 | 0.463 | ? | 0.366 | 0.666 | 0.448 |
| | 130 | ? | 0.240 | 0.353 | 0.404 | ? | 0.260 | 0.346 | 0.450? |
| 13 | 0 | 0.16 | 0.347 | 0.613 | 0.443 | ? | 0.353 | 0.573 | 0.467 |
| | 130 | 0.18 | 0.353 | 0.707 | 0.420 | ? | 0.360 | 0.720 | 0.425 |
| 14 | 0 | 0.20 | 0.430 | 1.087 | 0.413 | 0.15 | 0.440 | 1.080 | 0.423 |
| | 130 | 0.24 | 0.433 | 1.033 | 0.426 | ? | 0.420 | 1.100 | 0.398 |
| 15 | 0 | 0.16 | 0.333 | 0.700 | 0.400 | ? | 0.370 | 0.680 | 0.448 |
| | 130 | 0.17 | 0.327 | 0.700 | 0.392 | ? | 0.300 | 0.673 | 0.366 |
| 16 | 0 | 0.16 | 0.400 | 0.560 | 0.535 | 0.14 | 0.300 | 0.560 | 0.403 |
| | 130 | 0.18 | 0.360 | 0.740 | 0.419 | 0.14 | 0.340 | 0.760 | 0.391 |
| 17 | 0 | 0.16 | 0.510 | 1.287 | 0.449 | 0.14 | 0.500 | 1.300 | 0.439 |
| | 130 | 0.16 | 0.420 | 1.060 | 0.407 | ? | 0.473 | 1.110 | 0.451 |
| 18 | 0 | 0.24 | 0.447 | 0.840 | 0.489 | 0.16 | 0.427 | 0.817 | 0.472 |
| | 130 | 0.20 | 0.400 | 0.813 | 0.443 | 0.18 | 0.400 | 0.800 | 0.448 |
| 19 | 0 | 0.24 | 0.367 | 0.710 | 0.436 | 0.16 | 0.387 | 0.720 | 0.458 |
| | 130 | 0.20 | 0.310 | 0.613 | 0.396 | ? | 0.337 | 0.623 | 0.427 |
| 20 | 0 | 0.14 | 0.420 | 1.080 | 0.404 | 0.12 | 0.427 | 1.080 | 0.411 |
| | 130 | 0.14 | 0.323 | 0.670 | 0.396 | 0.16 | 0.373 | 0.657 | 0.462 |

*Values represent averages of 3 to 5 measurements.

45 to 89 years, and they included seven men and three women. None had received digitalis for at least one month previous to this investigation. The general plan and procedure already described in the study of the normal subjects were followed in this group, except that in a few cases digitalization was carried out in less than five days because of clinical urgency.

## RESULTS

The results of the study of this group are summarized in Tables III and IV. From Table III it is apparent that the changes in P-R duration which accompanied the administration of digitalis in therapeutic doses were too small and too inconstant to serve as a measure of the effect of the drug. The value for "K" was fairly consistently, but not uniformly, shorter in Lead II when digitalis was administered; in Lead IV F the value for "K" after digitalis was unchanged in one case, became increased in two others, and was variably shortened in seven. Study of all the electrocardiograms in each patient's series, however, revealed a lack of progressive change in "K" with increasing doses of digitalis, from which it appeared that this feature did not offer a quantitative indicator of digitalization. In only two of the ten series of

TABLE IV

T-WAVE CHANGES FOLLOWING DIGITALIZATION OF PATIENTS WITH CONGESTIVE FAILURE

| PATIENT NO. | DIGITALIS PER CENT | T WAVES (MM.) | | | |
|---|---|---|---|---|---|
| | | I* | II | III | IV F |
| 11 | 0 | ±2.5 | -3.0 | +3.5 | - 2.0 |
| | 100 | ±2.0 | +1.0 | +2.0 | ± 1.0 |
| | 130 | ±3.0 | ±1.0 | ±2.0 | + 1.5 |
| 12 | 0 | -1.0 | -1.5 | -0.5 | + 2.0 |
| | 100 | -2.0 | -1.0 | -0.5 | + 1.0 |
| | 130 | +1.5 | +1.0 | -0.5 | + 1.0 |
| 13 | 0 | +1.0 | +1.5 | +0.5 | +11.5 |
| | 100 | +1.0 | +1.5 | ±0.5 | + 8.0 |
| | 130 | +1.5 | +1.5 | ±0.5 | +11.1 |
| 14 | 0 | +1.0 | +1.5 | 0.0 | ± 1.0 |
| | 100 | +1.0 | +2.0 | 0.0 | ± 2.0 |
| | 130 | +1.5 | ±1.0 | 0.0 | ± 1.5 |
| 15 | 0 | ±1.5 | +1.0 | +3.0 | + 3.5 |
| | 100 | -2.5 | +2.0 | +3.0 | ± 1.5 |
| | 130 | -3.5 | +1.5 | +3.0 | - 1.5 |
| 16 | 0 | ±2.0 | +1.5 | +2.0 | - 4.0 |
| | 100 | ±2.0 | +0.5 | +1.0 | - 4.0 |
| | 130 | ±2.0 | +0.5 | +1.0 | - 4.0 |
| 17 | 0 | -1.0 | +1.0 | +1.5 | - 4.5 |
| | 100 | -1.0 | 0.0 | +1.0 | - 4.0 |
| | 130 | -1.0 | ±0.5 | +1.0 | - 5.0 |
| 18 | 0 | +2.0 | +2.5 | -0.5 | + 6.5 |
| | 100 | +1.5 | +2.5 | +1.0 | + 2.0 |
| | 130 | +1.5 | +3.0 | +0.5 | + 2.0 |
| 19 | 0 | +1.0 | +1.0 | -1.0 | ± 1.5 |
| | 100 | ±1.5 | -2.0 | -3.0 | - 1.0 |
| | 130 | ±1.5 | -2.0 | -3.0 | - 1.5 |
| 20 | 0 | 0.0 | +1.0 | +0.5 | ± 2.0 |
| | 100 | -2.0 | -1.0 | +1.0 | - 2.0 |
| | 130 | -2.0 | -1.5 | +1.0 | - 1.5 |

*Numerals refer to leads.

electrocardiograms were the RS-T segments depressed below their original levels following digitalis. As may be seen from Table IV, the T wave lost amplitude in the records of three patients, and changed from positive to negative in three other cases following digitalis; in the tracings of four patients, on the other hand, T gained in positive amplitude in one or more leads. Similar irregular changes in T were observed in the study of the normal group (see Section I).

No exact correlation between specific electrocardiographic changes and the state of digitalization was seen in these series of records from unselected patients with heart disease. In all but three of the ten cases the original electrocardiograms already exhibited abnormalities of the RS-T segments and T waves, and these may have interfered with the development of digitalis effects.

## SECTION III

### EFFECTS OF DIGITALIS ON THE ELECTROCARDIOGRAMS OF FIFTY SELECTED PATIENTS WITH HEART DISEASE

In order properly to investigate the electrocardiographic effects of digitalis on patients with diseased hearts, it was considered necessary to eliminate those whose variety of heart disease was known to be commonly associated with abnormalities of the RS-T segments and T waves. Excluded on this basis were patients more than 50 years of age, and cases of angina pectoris or myocardial infarction. Subjects with hypertension and with lesions of the aortic valves were rejected because their electrocardiograms are known frequently to show RS-T and T-wave abnormalities resembling those caused by digitalis. Also discarded were the records of patients with active rheumatic myocarditis, acute infectious diseases, pericarditis from any cause, advanced renal failure, vitamin deficiency disease, pulmonary embolism, and undiagnosed disease. As a result of such a rigid selection, therefore, the "cardiac group" considered in this study was composed almost entirely of patients with chronic rheumatic heart disease without aortic valvulitis. The material which was finally considered acceptable for study comprised 113 electrocardiograms from 50 patients, and represented about 3.5 per cent of the records obtained in this laboratory from January, 1938, to July, 1940.

For convenience in handling the data, the electrocardiograms were classified as follows:

| CLASS | DESCRIPTION |
|---|---|
| N | Normal adult males |
| ND | Normal adult males, digitalized |
| S | Cardiac subjects with sinus mechanism, without digitalis and without failure |
| SF | Cardiac subjects with sinus mechanism, without digitalis, but in congestive failure |
| SD | Cardiac subjects with sinus mechanism, digitalized, but not in failure |
| SDF | Cardiac subjects with sinus mechanism, digitalized and in failure |
| A | Cardiac subjects with auricular fibrillation, without digitalis and not in failure |
| AF | Cardiac subjects with auricular fibrillation, without digitalis, but in failure |
| AD | Cardiac subjects with auricular fibrillation, digitalized, but not in failure |
| ADF | Cardiac subjects with auricular fibrillation, digitalized and in failure |

The following measurements were made in millimeters for all leads:

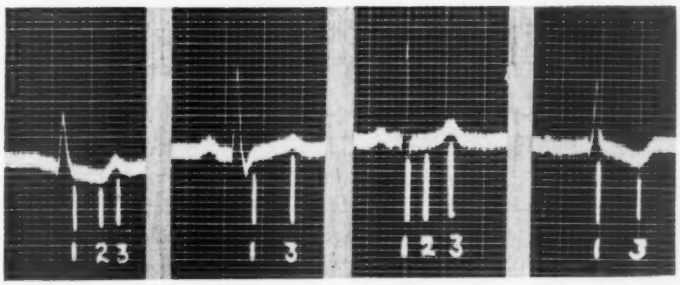
1. The level of the RS-T junction.

2. The level of the RS-T segments, if such a horizontal level existed (Fig. 1, *c*); otherwise, the height or depth to which this portion of the curve progressed before the formation of the T wave (Fig. 1, *a*). Often it was difficult, and sometimes impossible, to differentiate the com-

ponent parts of the RS-T segment and T wave, and the points then measured were taken where abrupt changes in direction occurred, as is illustrated in Fig. 1, *a*. Frequently there was no RS-T segment level (Fig. 1, *b*, *d*) and in the graphs (Fig. 2) the RS-T junction and the crest of T in such instances were joined by a straight line.

3. The amplitude and direction of T. When T was diphasic, the amplitude of the second phase was chosen.

These three points, together with the isoelectric line, were plotted for every electrocardiogram in each group, and the graphic results are presented in Fig. 2.




*a* *b* *c* *d*

Fig. 1.—Selected reference points for the graphic representation of the RS-T and T variations depicted in Fig. 2: *1*, level of RS-T junction; *2*, course of RS-T segment, or point of reversal in a diphasic wave, as in *a* (this feature is considered absent in tracings like *b* and *d*); *3*, amplitude of T wave, or second phase in a diphasic wave.

Although the criteria for selecting the electrocardiograms representing the "cardiac group" were intended to furnish records that were relatively free from RS-T and T-wave abnormalities which could be attributed to the heart disease itself, it was considered essential actually to establish the pre-digitalization characteristics for this group, rather than assume that they were normal. Accordingly, thirty-three records of patients who had not yet received digitalis were compared with the tracings of ten normal subjects (Section I), and the following minor differences were found:

TABLE V

| LEAD | ELECTROCARDIOGRAPHIC FEATURES | NORMAL (10 RECORDS) | CARDIAC (33 RECORDS) |
|---|---|---|---|
| I | Slight elevation of RS-T junction* | 30% | 3% |
| | Slight elevation of RS-T segment | 60% | 3% |
| II | Slight elevation of RS-T junction | 50% | 6% |
| | Slight elevation of RS-T segment | 80% | 9% |
| III | Upright T wave | 80% | 33% |
| IV F | Slight elevation of RS-T segment | 100% | 26% |

*Slight elevation means usually within the accepted normal limit of 1 mm.

*Comment.*—The electrocardiograms of the normal subjects showed elevation of the RS-T junction and segment (within the accepted normal limit of 1 mm.) in the majority of cases, whereas those of the cardiac group presented more nearly isoelectric RS-T segments. The T waves in

Leads I and II were upright in all. Our "cardiac group" was therefore regarded as acceptable for the study of digitalis effects. It is interesting, incidentally, that an isoelectric or negative T deflection in Lead III alone, although not considered abnormal, was decidedly more common in the group with heart disease.

The electrocardiographic changes after digitalization were studied in 80 records from patients with heart disease, and compared with the group of 33 tracings from patients who had not received the drug. The most significant differences were as follows:

TABLE VI

| LEAD | ELECTROCARDIOGRAPHIC FEATURES | NONDIGITALIZED (33 RECORDS) | DIGITALIZED (80 RECORDS) |
|---|---|---|---|
| II | Slight depression RS-T segment | 18% | 39% |
| | Inverted and isoelectric T waves | 3% | 34% |
| III | Slight depression RS-T segment | 6% | 25% |
| IV F | Slight depression RS-T segment | 5% | 31% |
| | Inversion of T wave | 0% | 10% |

*Comment.*—In only a minority of the records from digitalized patients were the RS-T segments lowered and the T waves inverted. Even these differences between the digitalized and the nondigitalized group were not, however, necessarily an effect of digitalis, for the treated group contained many more patients with grave heart disease, which might itself have introduced these abnormalities into the electrocardiogram.

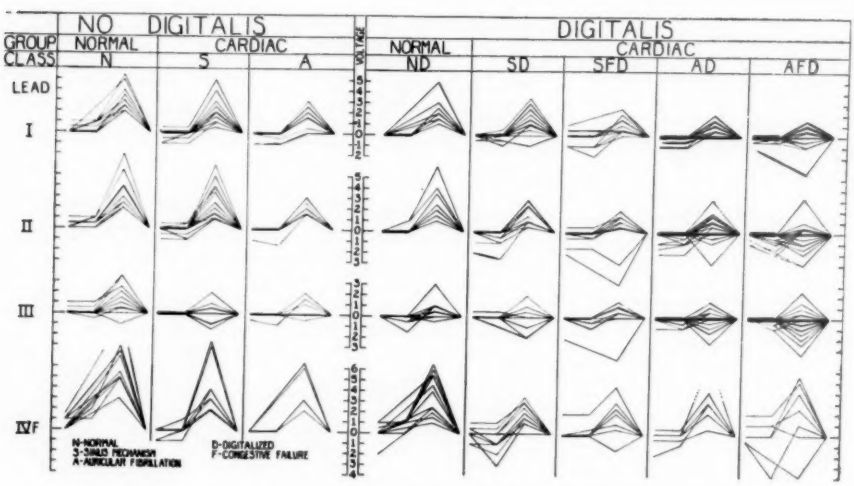



Fig. 2.—Graphic representations of RS-T segments and T waves in the various classes defined in Section III.

The above eighty tracings of digitalized patients included many who had auricular fibrillation, cardiac failure, or both. To eliminate the possible electrocardiographic effects of advanced heart failure and auricular fibrillation, a smaller group which was free from these complications was chosen for study. Twenty-nine electrocardiograms were available on patients with heart disease but no failure or abnormality

of rhythm. Approximately half of these records were from patients who were receiving digitalis. As may be seen from Fig. 2, classes *S* and *SD*, the direction of T in both these uncomplicated digitalized and non-digitalized groups was essentially the same. Although it is probable that the depression of the RS-T segment, which appeared particularly in Lead IV F, and the general loss in amplitude of the T waves were caused largely by the digitalis, the fact that these rather arbitrary changes were present in less than half the tracings detracts from their usefulness as quantitative indicators of digitalization.

Pursuing further the idea that T-wave inversion may be an expression of cardiac disease, rather than a digitalis effect, comparisons of various classes and combinations of classes of heart disease were made, and these data are presented graphically in Figs. 2 and 3 and in tabular form in Table VII.

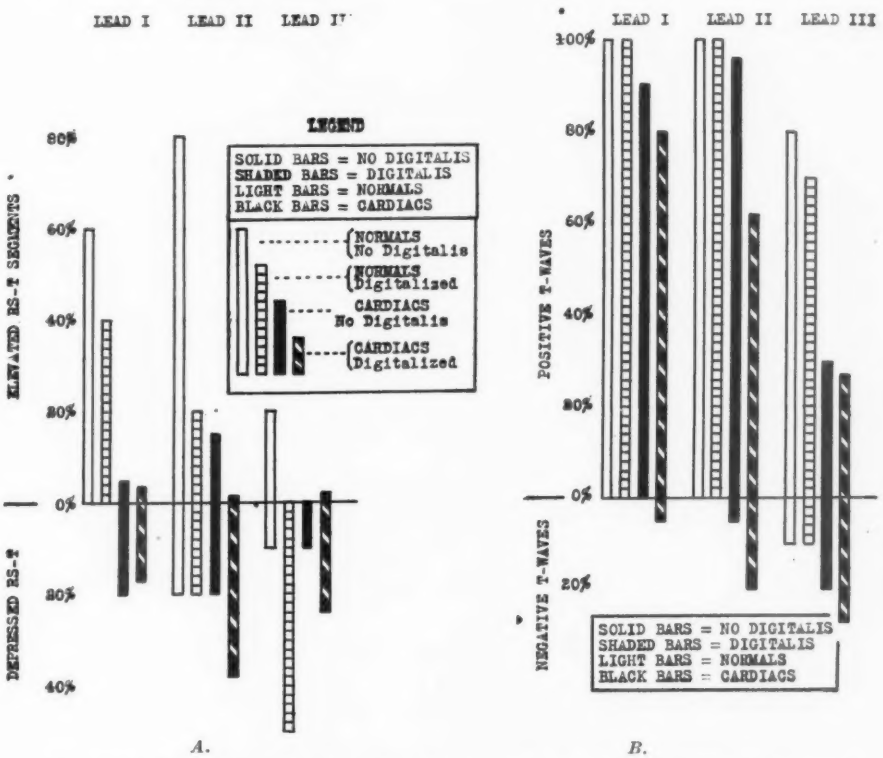



Fig. 3.—*A*, Frequency of elevation and depression of the RS-T segment, expressed in per cent. The difference between the sum of the positive and negative displacements and 100 per cent represents the incidence of isoelectric RS-T segments. *B*, Frequency of positive and negative T waves, expressed in per cent. The difference between the sum of the positive and negative waves and 100 per cent represents the incidence of isoelectric T waves.

Fig. 2 is designed to present in a quantitative, graphic form the composite picture of the RS-T and T features of the several heart disease classes. It is divided into a "No Digitalis" and "Digitalis" section, each of which is subdivided into selected classes of cardiac disease, ar-

TABLE VII

| CLASS | | LEAD I | | | | | | LEAD II | | | | | | LEAD III | | | | | | LEAD IV F | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | RS-T | | | T | | | RS-T | | | T | | | RS-T | | | T | | | RS-T | | | T | | |
| | | + | 0 | - | + | 0 | - | + | 0 | - | + | 0 | - | + | 0 | - | + | 0 | - | + | 0 | - | + | 0 | - |
| N* | | 60† | 40 | 0 | 100 | 0 | 0 | 80 | 20 | 0 | 100 | 0 | 0 | 20 | 70 | 10 | 80 | 10 | 10 | 100 | 0 | 0 | 100 | 0 | 0 |
| ND | | 40 | 60 | 0 | 100 | 0 | 0 | 20 | 80 | 0 | 100 | 0 | 0 | 0 | 50 | 50 | 70 | 20 | 10 | 90 | 10 | 0 | 100 | 0 | 0 |
| S | (15)‡ | 7 | 80 | 13 | 100 | 0 | 0 | 7 | 73 | 20 | 100 | 0 | 0 | 0 | 100 | 0 | 40 | 20 | 40 | 20 | 80 | 0 | 100 | 0 | 0 |
| A | (10) | 0 | 80 | 20 | 90 | 10 | 0 | 0 | 90 | 10 | 100 | 0 | 0 | 0 | 90 | 10 | 30 | 60 | 10 | 20 | 80 | 0 | 80 | 20 | 0 |
| AF | ( 6) | 0 | 83 | 17 | 83 | 17 | 0 | 0 | 67 | 33 | 83 | 0 | 17 | 0 | 83 | 17 | 17 | 67 | 17 | 50 | 50 | 0 | 100 | 0 | 0 |
| Total | (31) | 3 | 82 | 15 | 94 | 6 | 0 | 9 | 75 | 18 | 97 | 0 | 3 | 0 | 94 | 6 | 33 | 43 | 24 | 26 | 68 | 5 | 95 | 5 | 0 |
| SD | (14) | 7 | 79 | 14 | 86 | 7 | 7 | 0 | 57 | 43 | 100 | 0 | 0 | 7 | 64 | 29 | 21 | 22 | 57 | 20 | 30 | 50 | 90 | 10 | 0 |
| SFD | (10) | 20 | 40 | 40 | 90 | 10 | 0 | 10 | 50 | 40 | 80 | 0 | 20 | 0 | 50 | 50 | 60 | 30 | 10 | 30 | 70 | 0 | 70 | 15 | 15 |
| AD | (25) | 0 | 90 | 10 | 75 | 25 | 0 | 0 | 70 | 30 | 70 | 20 | 10 | 0 | 85 | 15 | 25 | 50 | 25 | 10 | 60 | 30 | 100 | 0 | 0 |
| AFD | (31) | 0 | 85 | 15 | 70 | 15 | 15 | 0 | 65 | 35 | 40 | 30 | 30 | 0 | 80 | 20 | 20 | 45 | 35 | 38 | 25 | 37 | 75 | 0 | 25 |
| Total | (80) | 3 | 83 | 14 | 78 | 16 | 6 | 1 | 60 | 39 | 66 | 16 | 18 | 1 | 74 | 25 | 25 | 44 | 31 | 28 | 44 | 31 | 84 | 6 | 10 |

*The *Class* designations are defined in the second paragraph of Section III.

†Figures indicate per cent of records showing these features.

‡The parenthetical figures indicate the number of records represented.

ranged from left to right in an approximate order of increasing abnormality of cardiac function. Inspection of the several classes enables one to observe the probable effects of digitalis, heart disease, auricular fibrillation, and congestive failure upon the RS-T segments and T waves. Table VII represents an analysis of the positive and negative deviations of RS-T and T, and shows the frequency of these deviations in the several heart disease classes.

Examination of Fig. 2 and Table VII, with particular attention to the RS-T segments and T waves, reveals several interesting facts bearing on the effect of digitalis. For example, although depression of the RS-T segment in Lead II was not observed in normal subjects even when they were digitalized, it was already present in 20 per cent of the cardiac patients *before digitalis* was given, and this incidence rose to but 40 per cent when the patients were receiving digitalis. Depression of the RS-T segment in Lead III was found in 50 per cent of the normal digitalized subjects, but in only 25 per cent of the digitalized cardiac patients who did not have failure. Depression of the RS-T segment in Lead IV F appeared in about one-third of the tracings, and seemed, in this lead alone, to be entirely a manifestation of digitalis effect in our "selected cardiac group." In Lead I there was little or no change in this segment following digitalis.

A negative T deflection was rare in Lead I in the digitalized group. In Lead II, inverted T waves occurred infrequently (20 per cent), and almost exclusively in classes complicated by heart failure, regardless of the presence or absence of the digitalis factor. The high incidence of isoelectric T waves in the cases of auricular fibrillation was due, in large part, to the difficulty in measuring T in the presence of coarse fibrillary waves. No positive statement can be made concerning the direction of the T waves in Lead III. It is apparent that flattening or inversion of the T wave seemed to be an expression of heart disease more than of digitalization in any of these classes; this fact is graphically portrayed in Fig. 3.

The presence of auricular fibrillation, unlike congestive failure, was not associated with a greater abnormality of the RS-T segment and T wave, nor did digitalis in the presence of this mechanism show more pronounced effects.

It appears from these observations that, although the electrocardiogram may reveal more or less characteristic changes attributable to digitalis, such effects are inconstant and unpredictable; that similar changes may result from abnormal cardiovascular states aside from digitalis influence; and that the electrocardiogram has, therefore, no general clinical value as a *quantitative* measure of digitalization in the therapeutic range.

## SUMMARY AND CONCLUSIONS

Progressive digitalization of ten normal subjects produced electrocardiographic changes which were too small in degree and too incon-

stant in character to indicate any quantitative correlation between the amount of the drug administered and the resultant electrocardiographic effects.

Similar results were obtained in a parallel investigation of ten unselected patients with heart disease and congestive failure.

The study was extended to include more than 100 electrocardiograms from a group of fifty patients who were carefully selected with the expectation that their electrocardiograms would be relatively free from RS-T and T-wave abnormalities which could be attributed to the heart disease itself.

It was observed: (1) that depression of the RS-T segments, with, perhaps consequent, loss in amplitude of the T waves, occurred in less than half of the electrocardiograms of the selected, digitalized patients; (2) that the onset and progression of such changes were neither constant nor uniform accompaniments of the administration of digitalis, and were not quantitatively indicative of the amount of the drug that had been given; (3) that heart disease itself resulted in abnormality of the RS-T segment and T wave quite independent of digitalis effects. This would, of course, have been much more striking if our "cardiac group" had not been selected in such a way as to exclude patients with those lesions which characteristically cause such abnormalities.

We conclude that the electrocardiogram has no practical clinical value for the *quantitative* estimation of the digitalis saturation of patients.

## REFERENCES

1. Cohn, A. E., Fraser, F. R., and Jamieson, R. A.: The Influence of Digitalis on the T Wave of the Human Electrocardiogram, J. Exper. Med. **21**: 593, 1915.
2. White, P. D., and Sattler, R. R.: The Effect of Digitalis on the Normal Human Electrocardiogram, With Especial Reference to A-V Conduction, J. Exper. Med. **23**: 613, 1916.
3. Pardee, H. E. B.: The Standardization of Digitalis by Its Action on the Human Heart, J. A. M. A. **81**: 186, 1923.
4. Larsen, K., Neukirch, F., and Nielsen, N. A.: Electrocardiographic Changes in Normal Adults Following Digitalis Administration, AM. HEART J. **13**: 163, 1937.
5. Stewart, H. J., and Watson, R. F.: The Effect of Digitalis on the Form of the Human Electrocardiogram, With Special Reference to Changes Occurring in the Chest Lead, AM. HEART J. **15**: 604, 1938.
6. Levy, H., and Boas, E. P.: Clinical Studies of Gitalin and of Digitalis in the Treatment of Auricular Fibrillation, AM. HEART J. **15**: 643, 1938.
7. Cheer, S. N., and Dieuaide, F. R.: Studies on the Electrical Systole ("Q-T" interval) of the Heart. III. The Effect of Digitalis on Its Duration in the Normal Heart, Chinese J. Physiol. **5**: 217, 1931.
8. Strauss, H., and Katz, L. N.: Effect of Digitalis on the Appearance of Lead IV, AM. HEART J. **10**: 546, 1934.
9. Geiger, A. J.: Digitalis U.S.P.XI. Recent Changes in Potency and Designation, Connecticut M. J. **4**: 331, 1940.
10. Standardization of Precordial Leads; Joint Recommendations of the American Heart Association and the Cardiac Society of Great Britain and Ireland, AM. HEART J. **15**: 107, 1938.
11. Ashman, R., and Hull, E.: Essentials of Electrocardiography: Appendix, New York, 1937, The Macmillan Co.

# VARIABLE INTERVAL BETWEEN ELECTRIC AND ACOUSTIC PHENOMENA IN AURICULAR FIBRILLATION

ALDO LUISADA, M.D.
WALTHAM, MASS.

THE time relation between the initial wave of the electrocardiogram and the first heart sound has been studied by many authors, in normal subjects and in patients, and the results have varied considerably. Lewis[1] says that the first sound begins 0.002 to 0.026 sec. after the beginning of R, and 0.011 to 0.039 sec. after the beginning of Q, with a very wide range of time. Lewis' study was done on patients with mitral stenosis and is quoted first because all three patients that I have studied had this disease. In normal subjects, Wiggers and Dean[2] found that the initial vibrations of the first sound occurred 0.01 to 0.02 sec. after the beginning of R in Lead II, never before the peak of R, and even 0.03 to 0.045 sec. after this peak. Among the recent authors, Cossio[3] says that the first sound starts with the apex of R, or 0.01 sec. after it. Calo[4] says that it can start from 0.02 sec. before the beginning of R to 0.05 sec. afterwards. Leblanc[5] gives figures of 0.02 to 0.04 sec. after the beginning of the QRS complex, and Caeiro and Orías[6] 0.008 sec. before the peak of R.

From a short review of the literature it is easy to see that the time relation between initial wave of the electrocardiogram and first sound may vary within a wide range, in normal people as well as in patients. Until now, however, it was thought that, in the same patient under the same conditions, the relation between electric and acoustic manifestations of ventricular systole was fixed, or at least could show only minimal changes. A study of one patient with mitral stenosis showed, on the contrary, some interesting features that will be described below. Therefore, the same study was later repeated on two other patients. The first patient, who showed the more marked changes which are the object of this study, was a 40-year-old man with mitral stenosis, slight heart failure, and auricular fibrillation. The other two patients, who were chosen as controls, were 38 and 48 years of age, respectively, and both had mitral stenosis, slight heart failure, and auricular fibrillation. The study was accomplished with a Stetho-Cardiette (Sanborn). Recording of the standard leads and of the heart sounds from different areas of the precordium was followed, in the third case, by simultaneous recording of heart sounds and venous pulse, and of heart sounds and arterial pulse.

From the Department of Cardiology of the Middlesex University, Waltham, Mass.
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### OBSERVATIONS IN THE FIRST CASE

Even a casual glance at the record of this patient (Fig. 1) shows that the QRS wave is followed by the first sound after a time which is quite different in the different systoles. Because the slow, initial vibrations of the first sound were confused with the vibrations caused by the diastolic murmur when diastole was short, it was possible only to measure the distance between apex of the Q wave and beginning of the ample, quick vibrations of the first sound. This distance varied from 0.03 to 0.07, and was sometimes more than twice that of the other systoles (see Table I). By measuring the distance between the first,

TABLE I

(THE FIRST PART REFERS TO FIG. 1, THE REST TO ANOTHER RECORD, NOT REPRODUCED; BOTH ARE FROM CASE 1.)

| | DISTANCE IN SECONDS BETWEEN THE PRECEDING R WAVE AND THE R WAVE STUDIED (SYSTOLE & DIASTOLE) | DISTANCE IN SECONDS BETWEEN THE APEX OF THE R WAVE AND THE FIRST QUICK VIBRATION OF THE FIRST SOUND (DELAY) | DISTANCE IN SECONDS BETWEEN THE FIRST QUICK VIBRATION OF THE FIRST SOUND AND THE FIRST QUICK VIBRATION OF THE SECOND SOUND (SYSTOLE) |
|---|---|---|---|
| 1. | ---- | 0.030 | 0.310 |
| 2. | 0.75 | 0.030 | 0.320 |
| 3. | *0.47* | *0.070* | *0.220* |
| 4. | *0.43* | *0.070* | *0.220* |
| 5. | ---- | 0.030 | 0.280 |
| 6. | 0.68 | 0.040 | 0.300 |
| 7. | 0.76 | 0.020 | 0.300 |
| 8. | 0.74 | 0.035 | 0.320 |
| 9. | *0.44* | *0.060* | 0.235 |

large, quick vibration of the first sound and the first, large, quick vibration of the second sound, i.e., the length of ventricular systole, it was found that this, too, changed from 0.31 to 0.22 sec. When diastole was long, the R wave was followed by a short interval before the first sound, and by a long systole. On the contrary, when diastole was short, the R wave was followed by a delayed first sound, and by a short systole. The shortening of systole was such that even by adding the longer delay it could not reach the length of the normal systole.

### OBSERVATIONS IN THE SECOND AND THIRD CASES

In the second case, the first sound started with one or two slow vibrations which were quite distinct from those of the diastolic murmur, even when diastole was short. It was possible, therefore, to calculate a double figure, i.e., that from the apex of Q to the beginning of the slow vibrations, and that from the apex of Q to the beginning of the quick vibrations. The result is shown in Fig. 2 and in Table II. When the diastole which preceded QRS was long, the time between the electric and acoustic waves was short. On the contrary, when diastole was short, the delay became longer. This fact was less evident than in Case 1,

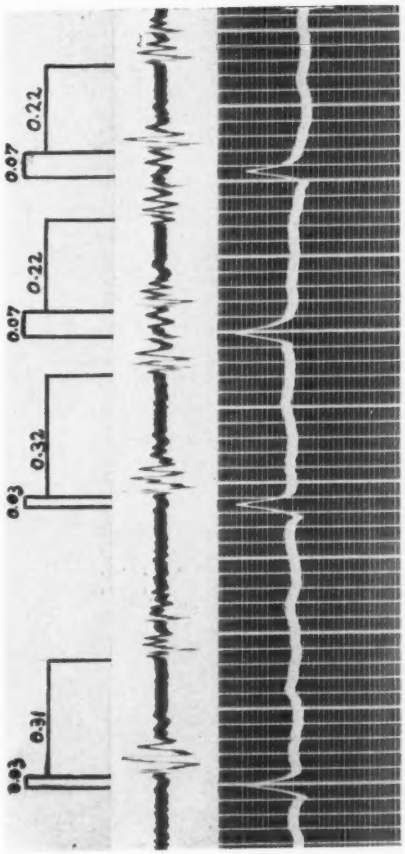


Fig. 1.—First patient, aged 40. Upper curve: Heart sounds, with usual microphone at the third left intercostal space. Lower curve: Lead II of the EKG. First sound delay and length of systole are marked on the top.

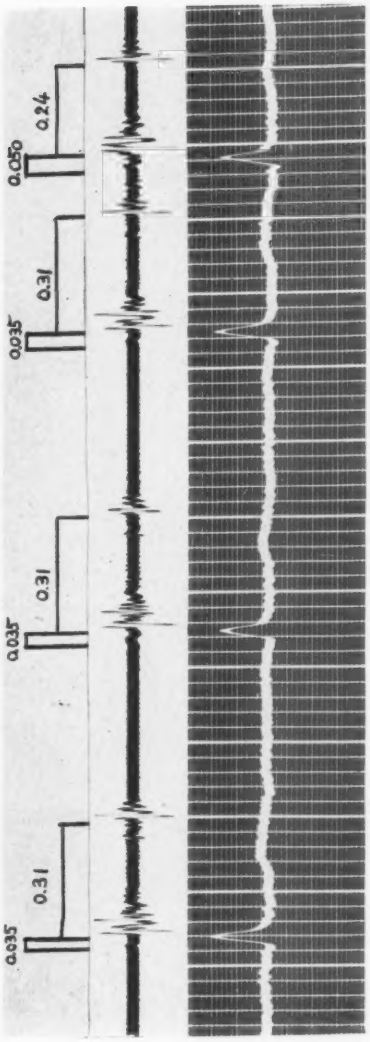


Fig. 2.—Second patient, aged 38. Upper curve: Heart sounds, with special microphone at the apex. Lower curve: Lead I of the EKG. Indications as in Fig. 1.

but was still present, as well for the slow as for the quick vibrations. The length of systole was also markedly shorter when the preceding diastole was shorter.

In the third case, the time between the Q wave and the first sound was practically the same in all systoles, and even the length of the systoles showed only slight changes in spite of the arrhythmia (Fig. 3, Table II).

TABLE II

(THE FIRST PART CONCERNS CASE 2, AS SHOWN IN FIG 2; THE SECOND PART CONCERNS CASE 3, AS SHOWN IN FIG. 3.)

| | DISTANCE IN SECONDS BETWEEN THE PRECEDING R WAVE AND THE R WAVE STUDIED (SYSTOLE & DIASTOLE) | DISTANCE IN SECONDS BETWEEN THE FIRST VIBRATION OF THE FIRST SOUND AND THE APEX OF THE Q WAVE (DELAY) | | DISTANCE IN SECONDS BETWEEN THE FIRST QUICK VIBRATION OF THE FIRST SOUND AND THE FIRST QUICK VIBRATION OF THE SECOND SOUND (SYSTOLE) |
|---|---|---|---|---|
| | | SLOW VIBRAT. | QUICK VIBRAT. | |
| 1. | ---- | -0.02 | +0.035 | 0.31 |
| 2. | 0.82 | -0.02 | +0.035 | 0.31 |
| 3. | 0.80 | -0.02 | +0.035 | 0.31 |
| 4. | *0.47* | *0.00* | *+0.050* | *0.24* |
| 1. | ---- | | 0.060 | 0.28 |
| 2. | 0.96 | | 0.060 | 0.28 |
| 3. | 0.60 | | 0.070 | 0.27 |
| 4. | 0.62 | | 0.060 | 0.28 |
| 5. | 0.61 | | 0.065 | 0.26 |

These facts made it possible to check up on the occurrence of an interesting feature of the pulse. It is known that in cases of auricular fibrillation the pulse is typically irregular, and that the waves travel with different speeds. When the delay between QRS and the peripheral pulse was measured, it was found to be longer for the smaller waves than for the others. My observation of a difference in the delay between QRS and first sound suggests that the delay between QRS and pulse was the result of a real delay in the mechanical part of systole, and not of a slower speed of the wave. Fig. 4 shows that the second wave, which was much smaller, had a longer delay after the first sound than the other waves. Therefore, the slower speed of the smaller waves was real, and not an artifact.

## DISCUSSION

The observation that there was a difference in the delay between QRS and the first sound in the different systoles of a patient with auricular fibrillation led to an investigation of two other patients of a similar age, with the same functional disability and the same heart lesion. The variability of the delay occurred in a lesser degree in the second case, and not at all in the third. One explanation is that, when diastole is shorter, the first sound has a different type of vibrations because the isometric

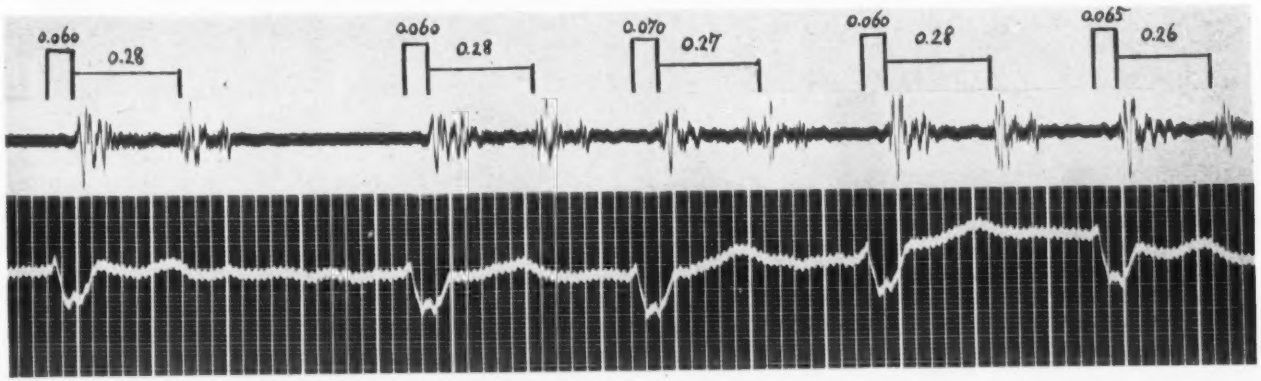


Fig. 3.—Third patient, aged 48. Upper curve: Heart sounds, with usual microphone at the third left intercostal space. Lower curve: Lead I of the EKG. Indications as in Fig. 1.

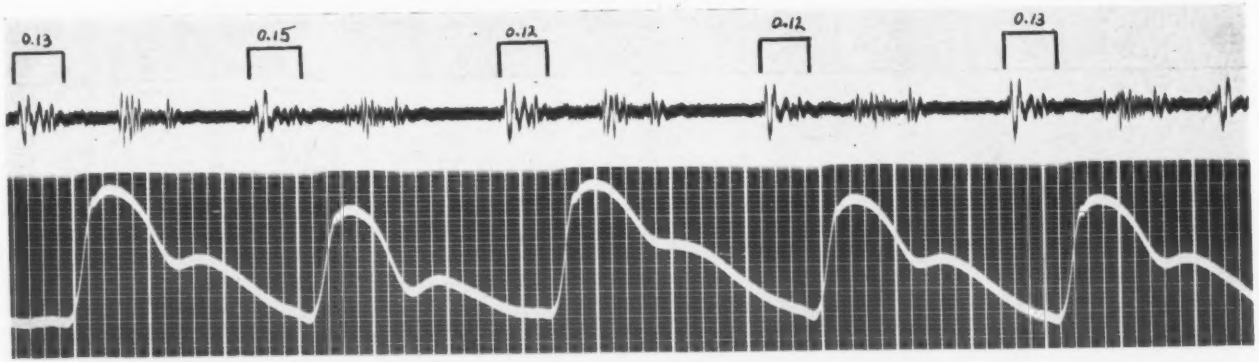


Fig. 4.—Third patient. Upper curve: Heart sounds at the aortic area. Lower curve: Brachial pulse. First sound-brachial pulse delay is marked.

contraction of the ventricles is longer. It could be supposed that the first, slow vibrations would be more prolonged, and that only the quick, high vibrations would be delayed. A study of this was not possible in the first case, but in the second case, in which there was also some change in the delay, a complete study was made, and showed a similar delay in the slow vibrations. The suggestion was at best only hypothetical, because the quick vibrations are already occurring during the isometric contraction of the ventricles (Orías and Braun Menéndez[7]).* We shall admit, then, that, in some cases of auricular fibrillation, when diastole is very short, the contraction of the ventricles is slightly delayed. This differing relationship between the electric and acoustic waves seems to point to the possibility of a dissociation between excitation and contraction of the ventricles. When this occurs it has a useful effect, for it allows longer filling of the ventricles when diastole is very short.

We also studied the length of ventricular systole, as shown by the distance between the first and second sounds. It was observed that, in Cases 1 and 2, systole was short when the preceding diastole was shorter. This well-known difference, which seems quite logical, is, however, not constant, as it was not present in Case 3. It can be suggested that, in some cases, part of the diastole is not accompanied by real filling of the ventricles, as most of it occurs during the early phase of quick filling. Differences in the length of diastole could then be accompanied by a nearly constant filling of the ventricles, and by a nearly constant length of the systoles.†

The speed of transmission of the pulse waves was studied only in the third case, for in this case there were no great differences in the delay between excitation and contraction of the ventricles. Moreover, inasmuch as the speed of the smaller pulse waves was slower, it is clear that that fact could not be attributed to the phenomenon which is newly described here.

## SUMMARY

A case of auricular fibrillation in which the interval between QRS and the first heart sound was much longer after a short diastole is described.

Two more cases were studied, in one of which the same phenomenon occurred. The length of systole changed in proportion to that of the preceding diastole in the two cases in which the interval between the electric and acoustic phenomena was variable.

Measurement of the pulse wave speed by means of the heart sounds does not change the known fact that smaller waves have a slower speed in cases of auricular fibrillation.

*Moreover, in some systoles the slow vibrations started before the Q wave. It is, therefore, probable that they were caused by some presystolic vibration of the mitral valve, unless an isoelectric phase of QRS was present.

†The observation that the length of the interval between the first and second sound changes often in auricular fibrillation was first made by Battaerd.[8] In his tracings the interval varied between 0.28 and 0.34 sec.

REFERENCES

1. Lewis, T.: The Time Relations of Heart Sounds and Murmurs With Special Reference to the Acoustic Signs in Mitral Stenosis, Heart 4: 241, 1912/1913.
2. Wiggers, C. J., and Dean, A. L.: The Nature and Time Relations of the Fundamental Heart Sounds, A. J. Physiol. 42: 476, 1917.
3. Cossio, P.: Aparato circulatorio, Buenos Aires, El Ateneo, 1939.
4. Calo, A.: Atlas de Phonocardiographie Clinique, Paris, Masson et cie, 1938.
5. Leblanc, M. A.: Quoted by Orías and Braun Menéndez.
6. Caeiro, A., and Orias, O.: Rev. Arg. de Cardiol. 4: 71, 1937.
7. Orías, O., and Braun Menéndez, E.: The Heart Sounds in Normal and Pathological Conditions, London, Oxford Univ. Press, 1939.
8. Battaerd, P. Y. T. A.: Further Graphic Researches on the Acoustic Phenomena of the Heart in Normal and Pathological Conditions, Heart 6: 121, 1915/17.
9. Lian, C., and Welti, J. J.: Le premier bruit du coeur normal, Arch. d. mal. du coeur. 31: 320, 1938.
10. Weiss, O., and Joachim, G.: Die Beziehungen der Herztöne und Herzgeräusche zum EKG. Deut. med. Woch. 36: 2187, 1910 (II).
11. Wolferth, C. C., and Margolies, A.: The Influence of Auricular Contraction on the First Sound and the Radial Pulse, Arch. Int. Med. 46: 1048, 1930.
12. Frédéricq, H.: Aspects actuels de la Physiologie du Myocarde. Paris, Presses Univ., 1927.

# FURTHER OBSERVATIONS ON THE EFFECTS OF CERTAIN XANTHINE COMPOUNDS IN CASES OF CORONARY INSUFFICIENCY, AS INDICATED BY THE RESPONSE TO INDUCED ANOXEMIA

NORMAN E. WILLIAMS, M.D., HENRY A. CARR, M.D.,
HOWARD G. BRUENN, M.D., AND ROBERT L. LEVY, M.D.
NEW YORK, N. Y.

IN A PREVIOUS paper[1] a method was presented for studying the effect of various drugs on the coronary circulation in man. The patients breathed a mixture of 10 per cent oxygen and 90 per cent nitrogen for twenty minutes, or until the complaint of discomfort made it desirable to terminate the induced anoxemia. The time of appearance of pain and the sum of the deviations of the RS-T segments of the four-lead electrocardiogram were compared in controls and after medication was given. The report was based on observations made in ten cases of coronary insufficiency.

One of the drugs studied was theophylline with ethylenediamine (aminophyllin). It was found that after its administration, either by vein or orally, the time of appearance of pain during induced anoxemia was materially prolonged, and RS-T deviation was diminished. The T waves of the electrocardiogram were also modified, but these changes were not subject to accurate quantitative comparative measurement and therefore were disregarded. It was concluded that aminophyllin, when taken by mouth in adequate doses, exerts a beneficial action in certain cases of cardiac pain by causing dilatation of the coronary vessels. The result, it was stated, probably depends, in part, upon the anatomic and physiologic state of the coronary circulation. These vary in different patients, and in the same person from time to time.

The literature dealing with the therapeutic action of the xanthines in cases of disease of the coronary arteries, and on coronary blood flow in experiments on animals, was reviewed. Three relevant papers have since been published. Essex and his collaborators,[2] using the thermostromuhr, found that, after intravenous injection of aminophyllin in trained, unanesthetized dogs, the coronary flow was increased from 15 to 173 per cent. The degree of increase was not proportional to the size of the dose, which ranged from 11.5 to 32 mg. per kg. The duration of the effect was from two to twenty-four minutes after injection. Using a flow meter, Green,[3] confirming the work of a number of others, observed that the intravenous injection of 20 to 50 mg. of aminophyllin in dogs

From the Department of Medicine, College of Physicians and Surgeons, Columbia University, and the Medical Clinic of the Presbyterian Hospital.

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produced an increase in coronary flow which was due to coronary dilatation. In his opinion, the xanthines, like the nitrites, act as coronary dilators, but their effectiveness may be diminished by their concomitant augmentation of cardiac work. Stewart and Jack[4] injected aminophyllin intravenously in man, in doses of 0.48 Gm. The peripheral blood flow was increased for a few minutes. There was also an increase in cardiac output, of a degree sufficient to provide for the increase in peripheral flow, without redistribution of the circulating blood volume.

In view of the relatively small number of cases included in our previous study, and because it seemed desirable to make comparable observations on the action of other xanthine derivatives, the present work was undertaken. In addition to aminophyllin, which was given by mouth and by vein, the following drugs were included: Theophylline with sodium acetate, by mouth and by vein, and theobromine with sodium acetate, by mouth. As before, lactose, taken orally, and physiologic salt solution, given intravenously, served as controls.

## PROCEDURE

The tests were conducted as described in our earlier paper.[1] They were performed in the cardiologic laboratory, at least one hour after the last meal, with the room quiet and at a comfortable temperature. Before beginning, the patient rested on the bed for not less than twenty minutes. The tests were done, as nearly as possible, at weekly intervals. At least one control anoxemia test[5, 6] was done in every case before the drug study was begun. In five cases, such a test was given on completion of the drug series, and after all medication had been omitted for a week. No change was made in the customary mode of life of the patients, and they were permitted to continue the use of nitroglycerin for the relief of anginal attacks; but nitroglycerin was not taken for at least one hour preceding a test.

The patients were unaware of the nature of the preparations given. At the end of each week, during which a remedy was taken orally, the patient expressed his opinion as to its effect upon his attacks of pain, and reported any unpleasant symptoms. He was asked also whether there was any modification in his response to effort, how many nitroglycerin tablets were used, and whether any emotional or economic upsets had occurred which might have a bearing upon his condition. All of his answers were noted and charted.

## DRUGS AND DOSAGE

*Theophylline With Ethylenediamine (Aminophyllin).*—For oral use, this was put into capsules in the hospital pharmacy, each containing 0.18 Gm. (3 gr.).* One capsule was taken three times daily after meals for one week. In the previous study, the same amount was given four times a day. The dose for intravenous injection was 0.48 Gm. (7½ gr.) in 20 c.c. of normal salt solution.† The injection was made into a cubital vein during a five-minute period. An electrocardiogram was taken five minutes before the injection and another five minutes after its completion. The anoxemia test was then started.

*Made by Lederle Laboratories, Inc. This is said to contain not less than 70 per cent of theophylline.

†Made by Byk-Guldenwerke, Berlin, Germany, and called Metaphyllin. This was part of a pre-war supply on hand. The theophylline content is not stated on the package.

No drugs, except nitroglycerin as needed, were taken during the week preceding the intravenous injections. This rule obtained not only for aminophyllin, but for all substances given by vein.

*Theophylline With Sodium Acetate.**—Enteric-coated tablets were given orally three times a day after meals for one week. Each tablet contained 0.18 Gm. (3 gr.). During one week, the individual dose was one tablet; during a second week it was two tablets (0.36 Gm.). Intravenously, 0.48 Gm. in twenty c.c. of sterile salt solution was injected, using the same technique as described for aminophyllin.

*Theobromine With Sodium Acetate.*†—Enteric-coated tablets were given orally. During one week, one tablet of 0.45 Gm. (7½ gr.) was given four times daily, after meals and at bedtime. During a second week, two tablets (0.9 Gm.) were given three times daily after meals.

*Lactose.*—This was employed as a control for the drugs given by mouth. It was prepared in capsules of 0.2 Gm. each, resembling in appearance those containing aminophyllin. The patients received one capsule three times a day for a week, in each course.

*Physiologic Salt Solution.*—This served as a control for the drugs injected intravenously. In each case, 20 c.c. were given by vein, according to the technique described for aminophyllin.

## MATERIAL (TABLE I)

Observations were made on ten patients, three of whom were used as subjects in our previous drug study. In all, the diagnosis was coronary sclerosis with anginal pain. All of them were regarded as having moderately advanced disease, as indicated

TABLE I

CLINICAL MATERIAL

TEN PATIENTS WITH CORONARY SCLEROSIS AND ANGINAL PAIN

| CASE NO. | HOSPITAL UNIT NO. | AGE (YR.) | SEX | COLOR | ADDITIONAL DIAGNOSIS | CONTROL EKG. | CARDIAC ENLARGEMENT |
|---|---|---|---|---|---|---|---|
| 1 | 589726 | 66 | M. | Wh. | Hypertension | Normal | + |
| 2 | 295520 | 59 | F. | Col. | | Normal | + |
| 3 | 360149 | 65 | M. | Wh. | Healed myocardial infarct | Abnormal | + |
| 4 | 376063 | 70 | M. | Wh. | | Abnormal | 0 |
| 5 | 216669 | 55 | F. | Wh. | | Normal | 0 |
| 6 | 591058 | 57 | F. | Wh. | Hypertension | Normal | 0 |
| 7 | 367410 | 47 | M. | Wh. | | Normal | 0 |
| 8 | 477070 | 65 | M. | Wh. | | Normal | 0 |
| 9 | 285886 | 42 | M. | Wh. | Healed myocardial infarct | Normal | 0 |
| 10 | 357651 | 46 | F. | Col. | | Normal | 0 |

by the severity and frequency of attacks, as well as by physical and electrocardiographic examination. None of the patients suffered from congestive heart failure; and none was tested who had had an attack of coronary occlusion within four

*The tablets and the solution for intravenous injection were supplied by the Upjohn Company, through the kindness of Dr. A. Garrard Macleod. The theophylline content was said to be always 60 per cent of the labelled dose. Roentgen studies in man have shown that 91 per cent of 144 tablets passed through the stomach intact, and, of these, 91 per cent disintegrated in the small intestine. Only five entered the colon intact, and not one was recovered from the feces (Pharmaceutical Bulletin No. 113, prepared by the Upjohn Company). The composition of the enteric coating is not given.

†These tablets were supplied by Brewer and Company, Inc. The enteric coating, it is stated, is made of whale wax. Roentgen studies on man have shown that 97 per cent of the tablets disintegrate promptly in the first portion of the small intestine (personal communication from the Brewer Company). These tablets are said to contain not less than 63 per cent of theobromine.

months. They took no drugs, other than those prescribed for the study, during the period of these observations. They were chosen because they were well known to us, having been under observation in the outpatient department or in the hospital wards, or both, over a period of months or years. They were of average intelligence and were cooperative.

In age, they ranged from 42 to 70 years. Six were white men. Of four women, two were white and two colored. Two had healed myocardial infarcts; coronary occlusion had occurred at least a year before these tests were carried out. One man and one white woman had hypertension. During the latter part of the study, the woman, while at home, suffered from an attack of acute coronary occlusion, so that administration of several of the drugs had to be omitted in her case. Two men and one colored woman had enlarged hearts. All had had spontaneous attacks of anginal pain for at least six months; in each case, the oral use of nitroglycerin afforded a measure of relief. In eight, the control electrocardiogram was normal;

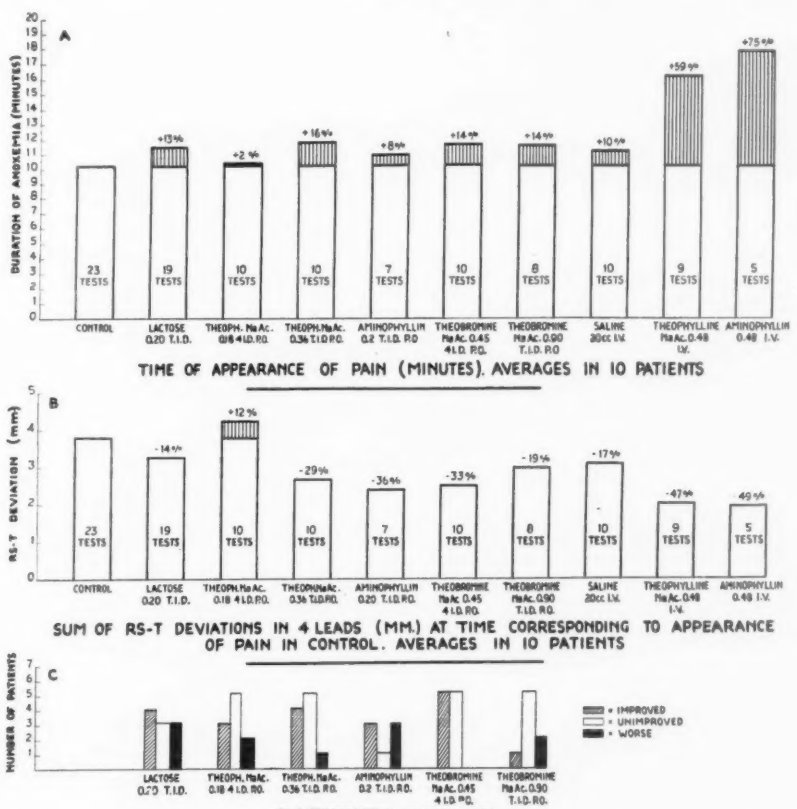


Fig. 1.—*A*, Modifying effect of drugs on the time of appearance of cardiac pain caused by induced anoxemia. *B*, Modifying effect of drugs on deviation of the RS-T segments caused by induced anoxemia. *C*, Modifying effect of drugs, orally administered, upon symptoms. Each drug was given for a period of one week.

in two it was abnormal. All showed positive control anoxemia tests.[5, 6] Eight of the ten experienced pain in less than twenty minutes during the control tests; two were able to breathe a 10 per cent oxygen mixture for the full period without discomfort, although significant changes occurred in the form of the electrocardiograms.

TABLE II

EFFECTS OF DRUGS, TAKEN BY MOUTH

| DRUG | INDIVIDUAL DOSE (GM.) | INDIVIDUAL TESTS (NUMBER) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | TIME OF ONSET OF PAIN | | | DEGREE OF RS-T DEVIATION | | | PATIENT'S SYMPTOMS | | |
| | | DELAYED | HASTENED | UNCHANGED | DECREASED | INCREASED | UNCHANGED | IMPROVED | WORSE | UNCHANGED |
| Aminophyllin | 0.20 | 3 | 3 | 1 | 6 | 1 | 0 | 3 | 3 | 1 |
| Theophylline with sodium acetate | 0.18 | 1 | 3 | 6 | 5 | 4 | 1 | 3 | 2 | 5 |
| Theophylline with sodium acetate | 0.36 | 5 | 3 | 2 | 9 | 0 | 1 | 4 | 1 | 5 |
| Theobromine with sodium acetate | 0.45 | 4 | 2 | 4 | 8 | 2 | 0 | 5 | 0 | 5 |
| Theobromine with sodium acetate | 0.90 | 2 | 4 | 2 | 6 | 2 | 0 | 1 | 2 | 5 |
| Lactose | 0.20 | 4 | 0 | 14 | 7 | 0 | 11 | 7 | 5 | 7 |

The results are based upon 105 tests and measurements of 775 four-lead electrocardiograms.*

## RESULTS (FIG. 1)

Because the functional state of the coronary circulation in a given person is subject to spontaneous variation, the results in the ten cases were pooled, averaged, and charted. In this way trends became apparent. The effects in the individual cases are also given in the text and in Table II.

*Theophylline With Ethylenediamine (Aminophyllin), by Mouth.*—Seven patients received this drug. In this group there was no significant delay in the onset of pain (8 per cent). The deviation of the RS-T segments was diminished by 36 per cent. In the individual cases, the onset of pain was delayed in three; it occurred earlier than in the control in three; and in one no change was noted. RS-T deviation was decreased in six cases and increased in one. In three instances the patient reported a lessening of symptoms during the week; in one there was no change; and in three the discomfort increased.

*Theophylline With Ethylenediamine, by Vein.*—This was given to five patients. In this group the onset of pain was delayed by 75 per cent. RS-T deviation was diminished by 49 per cent. In the individual cases, the onset of pain was delayed in three and occurred earlier than in the control in one. In the fifth case, the patient experienced no pain during the control test, or after receiving the drug. RS-T deviation was diminished in all five cases.

*Theophylline With Sodium Acetate, by Mouth. A. Dose—0.18 Gm., Four Times a Day.*—This was given to ten patients. In the group, there was no significant delay in the onset of pain (2 per cent). RS-T deviation was increased by 12 per cent. In the individual cases, the onset of pain was delayed in one; in three, pain occurred earlier than in the control; in six, there was no change. RS-T deviation was increased in five, decreased in 4, and unchanged in one. In three instances the patient reported lessening of symptoms; in five there was no change; and in two the discomfort increased.

*B. Dose—0.36 Gm., Three Times a Day.*—This was given to ten patients. In this group the onset of pain was delayed by 16 per cent. RS-T deviation was decreased by 29 per cent. In the individual cases, the onset of pain was delayed in five and occurred earlier than in the control in three, and in two there was no change. RS-T deviation was decreased in nine cases; no change was observed in one. In four instances the patient reported a lessening of symptoms; in five there was no change; and in one the discomfort increased.

*All four leads of the electrocardiogram were taken while pain was present, if it occurred. The complete record can be made in from one to two minutes, and prolongation of anoxemia for this length of time was found to be without hazard.

The precordial lead used was the one designated as IV F by the American Heart Association. All electrocardiograms were read independently by at least two observers.

*Theophylline With Sodium Acetate, by Vein.*—This was given to nine patients. In this group the onset of pain was delayed by 59 per cent. RS-T deviation was decreased by 47 per cent. In the individual cases, the onset of pain was delayed in seven; the other two patients were able to breathe the 10 per cent oxygen mixture for the full twenty minutes without discomfort. RS-T deviation was diminished in all of the nine cases.

*Theobromine With Sodium Acetate, by Mouth. A. Dose—0.45 Gm., Four Times a Day.*—This was given to ten patients. In this group the onset of pain was delayed by 14 per cent. RS-T deviation was decreased by 33 per cent. In the individual cases, the onset of pain was delayed in four; in two pain occurred earlier than in the control; and in four there was no change. RS-T deviation was decreased in eight and increased in two. In five instances, the patient reported improvement; in five there was no change; and in none was the discomfort increased.

*B. Dose—0.9 Gm., Three Times a Day.*—This was given to eight patients. In this group the onset of pain was delayed by 14 per cent. RS-T deviation was decreased by 19 per cent. In the individual cases, the onset of pain was delayed in two; it occurred earlier than in the control in four; and in two there was no change. RS-T deviation was decreased in six cases and increased in two. In only one instance did the patient report improvement; in five there was no change; and in two the discomfort increased.

*Lactose, by Mouth.*—This was given to ten patients on nineteen occasions. In the entire series of tests, the onset of pain was delayed by 13 per cent. RS-T deviation was decreased by 14 per cent. In the individual cases, the onset of pain was delayed in four tests on four patients. RS-T deviation was decreased in twelve tests on seven patients. In seven instances the patients reported improvement; in seven there was no change; and in five the discomfort increased.

*Physiologic Salt Solution, by Vein.*—This was given to ten patients. In this group the onset of pain was delayed by 10 per cent. RS-T deviation was decreased by 17 per cent. In the individual cases, the onset of pain was delayed in two; in three, pain occurred earlier than in the control; and, in five, there was no change. RS-T deviation was decreased in seven; in three there was no change.

### UNPLEASANT DRUG EFFECTS

The unpleasant symptoms ascribed by the patients to the various drugs, when they were taken orally, are shown in Table III. Insomnia, nausea, and abdominal discomfort were the most frequent complaints. In a dosage of 0.36 Gm. four times a day, theophylline with sodium acetate, in all but one case, caused so much insomnia and gastrointestinal distress that the evening dose was discontinued. For the same reason, the larger dose of theobromine with sodium acetate (0.9 Gm.) was re-

TABLE III

UNPLEASANT EFFECTS OF DRUGS TAKEN BY MOUTH

| DRUG | NUMBER OF PATIENTS | DOSAGE | UNPLEASANT EFFECTS | |
|---|---|---|---|---|
| | | | NUMBER OF PATIENTS COMPLAINING | SYMPTOMS |
| Aminophyllin | 7 | 0.20 Gm. t.i.d. | 3 | 1 anorexia<br>1 nausea<br>1 swelling and aching of face; aching of teeth and gums; nausea and vomiting |
| Theophylline with sodium acetate | 10 | 0.18 Gm. 4 i.d. | 4 | 2 anorexia<br>1 nausea; gas<br>1 insomnia; heartburn |
| Theophylline with sodium acetate | 10 | 0.36 Gm. t.i.d. | 5 | 2 insomnia; abdominal pain; gas<br>1 insomnia; abdominal pain; gas; vomiting<br>1 nausea; vomiting<br>1 swelling and aching of face; aching of teeth and gums; nausea and vomiting |
| Theobromine with sodium acetate | 10 | 0.45 Gm. 4 i.d. | 4 | 1 anorexia<br>1 nausea<br>1 flatulence; belching<br>1 palpitation |
| Theobromine with sodium acetate | 8 | 0.90 Gm. t.i.d. | 6 | 2 insomnia; abdominal discomfort<br>2 vomiting<br>1 insomnia<br>1 nausea; flatulence |
| Lactose | 10 (19 tests) | 0.20 Gm. t.i.d. | 3 | 1 nausea; vertigo<br>2 abdominal pain |

duced from four to three times daily. In one case (Case 6), both aminophyllin and theophylline with sodium acetate caused swelling and aching of the face, aching of the teeth and gums, and nausea and vomiting. The patient was not affected by theobromine sodium acetate. Apparently, in this instance, there was a true idiosynerasy to theophylline. This is a rare occurrence. Because of the severe toxic reaction, she was not given either of the theophylline preparations by vein.

On a number of occasions, after the intravenous injection of aminophyllin or theophylline with sodium acetate, the patients complained of a sense of warmth. No untoward reactions were encountered.

## DISCUSSION

It is of some practical importance to know whether therapeutic doses of the xanthine compounds dilate the coronary vessels in man, and so may be expected to afford relief to patients with anginal pain. That relatively large amounts, when injected intravenously into normal animals,

will cause an increase in coronary flow has been abundantly demonstrated. The evidence for a similar and more sustained effect in patients with coronary sclerosis who have taken various members of this group by mouth has been conflicting.

In our earlier study,[1] using the same objective method employed in the observations just described, it was demonstrated that aminophyllin exerted such an action. It is significant that, with this drug, the results with respect to the degree of RS-T deviation in 1939 and 1940 show such close agreement (Table IV). When given by vein, the decrease in RS-T deviation was 58 and 49 per cent; the delay in the onset of pain in the 2 series was, respectively, 63 and 75 per cent. When given by mouth, the decrease in RS-T deviation was 32 and 36 per cent; the delay in the onset of pain was, respectively, 26 and 8 per cent. The effect on pain was less in the 1940 series of patients, who suffered, as a group, from a more advanced state of disease. They received only three doses a day, as compared to four doses in the 1939 series. But, objectively, the degree of coronary dilatation produced, as indicated by decrease in RS-T deviation, was similar in the two groups.

Lactose, when given by mouth, caused a delay in the onset of pain, in the two series of cases, of 2 and 13 per cent respectively; the decrease in RS-T deviation was 13 and 14 per cent. This degree of variation in RS-T deviation, as previously pointed out,[1] must be regarded as the approximate error of the method.

Because of the similarity of these two sets of observations, we feel justified in stressing the significance of the effects of theophylline with sodium acetate and theobromine with sodium acetate which were noted under comparable circumstances. The delay in the onset of pain, as was the case in the 1940 group with aminophyllin, was not striking, but

TABLE IV

COMPARISON OF ACTION OF AMINOPHYLLIN AND LACTOSE IN STUDIES OF 1939 AND 1940

| DRUG | DATE | NUMBER OF TESTS | DELAY IN ONSET OF PAIN (PERCENTAGE CHANGE) | DECREASE IN RS-T DEVIATION IN EKG. (PERCENTAGE CHANGE) |
|---|---|---|---|---|
| Aminophyllin (by vein) | 1939 | 10 | 63 | 58 |
| | 1940 | 5 | 75 | 49 |
| Aminophyllin (by mouth) | 1939 | 14 | 26 | 32 |
| | 1940 | 7 | 8 | 36 |
| Lactose (by mouth) | 1939 | 10 | 2 | 13 |
| | 1940 | 18 | 13 | 14 |

the decrease in RS-T deviation produced by theophylline with sodium acetate, in individual doses of 0.36 Gm., and by theobromine with sodium acetate, in doses of 0.45 Gm., was comparable to that obtained with aminophyllin, namely, 29 and 33 per cent, respectively. Apparently, theophylline with sodium acetate in the smaller dose of 0.18 Gm. was ineffectual. The larger dose of theobromine with sodium acetate, 0.9 Gm., caused toxic effects in so many of the cases that the beneficial action, if any, was masked.

In general, patients with less severe and less frequent attacks of pain showed a better therapeutic response than those in the more advanced stages of illness. This was well exemplified in the same patient at different times (Fig. 2). This man had suffered from attacks of anginal pain for ten months before the first drug study was made, in 1938. At that time, walking slowly for a distance of one to four blocks induced characteristic discomfort which was relieved by nitroglycerin. On two

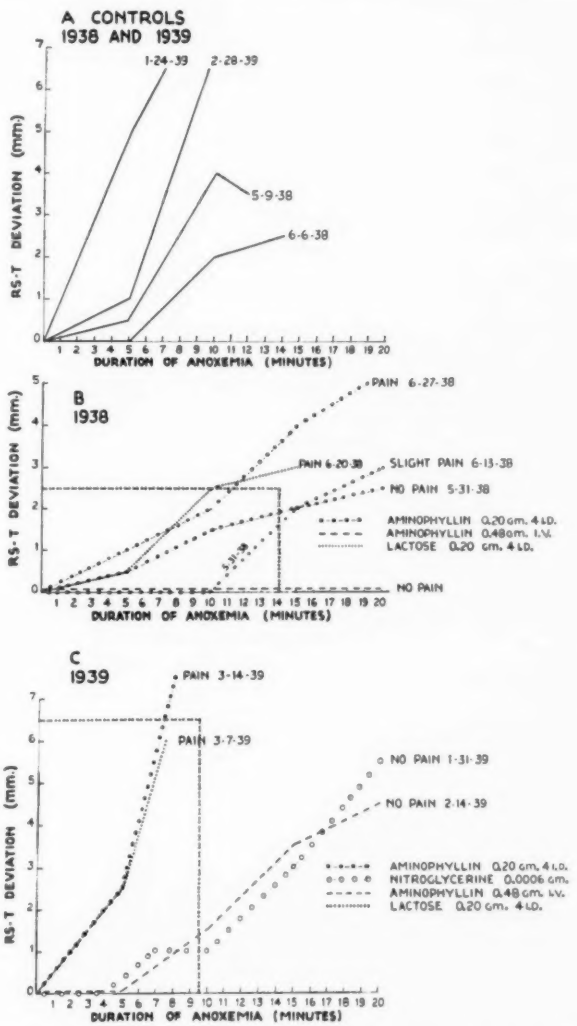


Fig. 2.—(Unit No. 542971) The response of a 54-year-old Japanese chef to induced anoxemia, with and without the modifying effects of drugs, during two studies made six months apart. He had had attacks of anginal pain for ten months. *A*, Control anoxemia tests. *B*, The modifying effect of lactose and aminophyllin during May and June, 1938. *C*, The modifying effect of lactose, nitroglycerin, and aminophyllin during January, February, and March, 1939. (The rectangle outlined by the broken lines, shown in Figs. 2, 3, 4, and 5, represents each patient's optimal response to induced anoxemia. It is derived by taking from the several control tests the longest time he could endure anoxemia and the smallest amount of RS-T deviation observed, regardless of whether they were noted in the same test.)

occasions, after taking aminophyllin for a week, the RS-T deviation was diminished, respectively, by 24 and 36 per cent. During these two weeks, the need for nitroglycerin decreased from four to ten tablets daily, to one or two a week. In January and February, 1939, his toler-

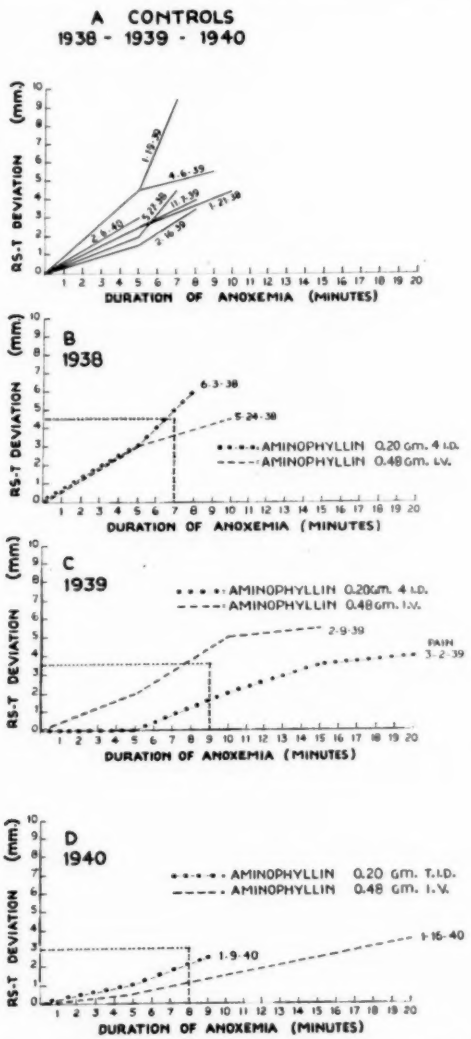


Fig. 3.—Case 4. (Unit No. 376063) The response of a 70-year-old, white, stationary engineer to induced anoxemia, with and without the modifying effect of drugs given in the course of three studies conducted over a period of two years. He had had attacks of anginal pain for eight years. *A*, Series of control tests performed in the period from January, 1938, to February, 1940. *B*, Modifying effect of aminophyllin in 1938. *C*, Modifying effect of aminophyllin in 1939. *D*, Modifying effect of aminophyllin in 1940.

ance for the 10 per cent oxygen mixture was less than it had been six months previously, and the modifying effects of aminophyllin were correspondingly diminished. In fact, at this time aminophyllin was wholly ineffectual by mouth, although it still exerted its action when injected

intravenously. He was aware of the change in his condition and complained that medication did not afford relief as it had the preceding summer.

In contrast to this decrease in effectiveness, coincident with aggravation of symptoms, are the records of the patient which are shown in Fig. 3. His response to anoxemia was studied in 1938, 1939,

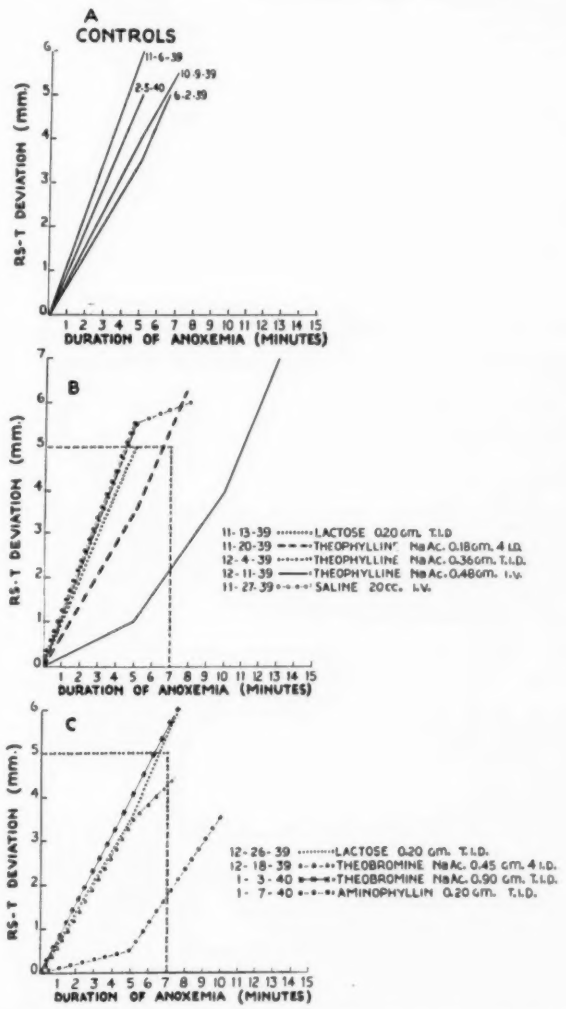


Fig. 4.—Case 9, (Unit No. 285886) The response of a 42-year-old, white, taxicab driver to induced anoxemia, with and without the modifying effect of drugs. He had had attacks of anginal pain for nine years. Myocardial infarction occurred in November, 1938. *A*, Control tests. *B* and *C*, Response to anoxemia, as modified by drugs.

and 1940. The effects of aminophyllin by mouth and by vein are charted. The rectangles marked off by the broken lines in B, C, and D show an increase in tolerance to the 10 per cent oxygen mixture during the period from 1938 to 1940. This is apparent from the progressive

decrease in RS-T deviation. Aminophyllin, when given intravenously, became gradually more effective; given by mouth, the same trend was apparent, but to a lesser degree. The patient's symptoms, as shown by his reaction to ordinary physical activity, showed no noteworthy change in the course of these two years; the responses to effort and to the action of the drug were not parallel. In Fig. 3*C*, it appears that when amino-

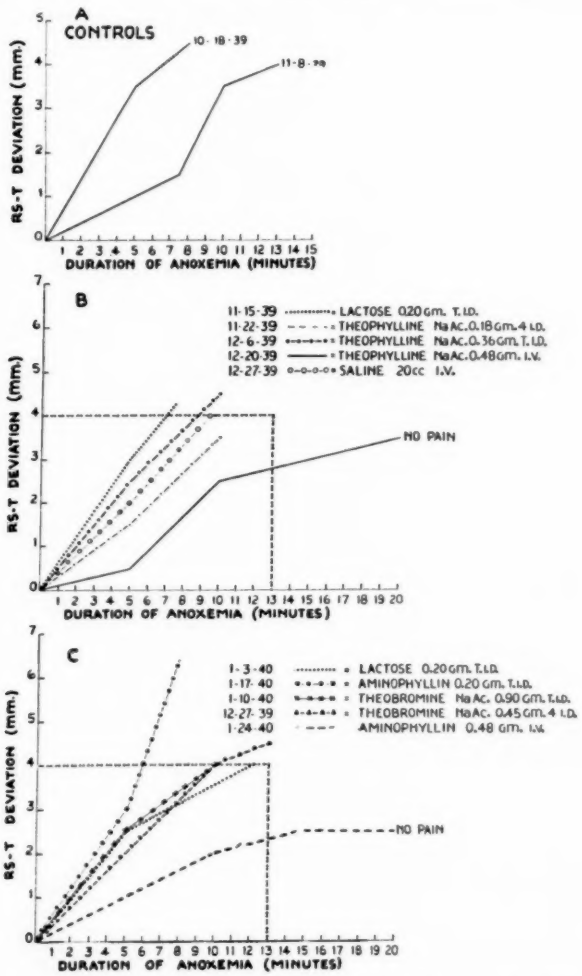


Fig. 5.—Case 7, (Unit No. 367410) The response of a 47-year-old, white, male cornet player to induced anoxemia, with and without the modifying effect of drugs. He had had attacks of anginal pain for six years. *A*, Control tests. *B* and *C*, Response to anoxemia, as modified by drugs.

phyllin was taken by mouth it was more effective than when injected intravenously. This unusual response was observed in two other cases. Its explanation is not clear.

None of the ten patients reacted favorably to all of the drugs; and none of the drugs, in any of the dosages employed, was effective in all

of the cases. The variation in the individual human reaction to various medicinal remedies is well known; it makes impossible the prediction of what the therapeutic result will be in any given instance. The character and extent of the lesions in the coronary arteries undoubtedly determine, in a measure, the effectiveness of treatment.

In Figs. 4 and 5 are charted the response in Cases 7 and 9 to each of the drugs studied. In Case 7, none of the drugs was effective by mouth, but aminophyllin, by vein, modified the response to anoxemia. Of the drugs taken orally by Patient 9, only aminophyllin exerted any demonstrable action.

From the point of view of ability to induce coronary dilatation, as shown by decrease in RS-T deviation, aminophyllin in individual doses of 0.20 Gm., theophylline with sodium acetate in doses of 0.36 Gm., and theobromine with sodium acetate in doses of 0.45 Gm. were about equally effective when given by mouth. None of them, in this series of cases, materially modified the time of appearance of pain caused by induced anoxemia. The effect on the patients' symptoms was variable and difficult to appraise accurately.

## SUMMARY AND CONCLUSIONS

1. Aminophyllin, theophylline with sodium acetate, and theobromine with sodium acetate were administered to ten patients with coronary sclerosis and anginal pain. The two theophylline compounds were given both orally and by vein; the theobromine derivative was given only by mouth. Lactose, given orally, and physiologic salt solution, injected intravenously, served as controls.

2. The response to induced anoxemia, employing a technique previously described, was used as an index of the action on the coronary circulation. The effects on the sum of the RS-T deviations in the four-lead electrocardiogram and on the time of appearance of pain were the criteria used; the former, because it was an objective index, was stressed as the more important.

3. Aminophyllin, in doses of 0.20 Gm., three times a day, theophylline with sodium acetate, in doses of 0.36 Gm., four times a day, and theobromine with sodium acetate, in doses of 0.45 Gm., four times a day, were about equally effective, when given orally, in causing a decrease in RS-T deviation. None of them, in this series of cases, materially modified the time of appearance of pain caused by induced anoxemia. In a previous study, aminophyllin, in doses of 0.2 Gm., given orally four times a day, delayed the time of onset of pain; the dose was larger and the symptoms and signs of coronary insufficiency in the former group of patients were not so marked.

4. After intravenous injection, the decrease in RS-T deviation and the delay in the onset of pain were about the same for equal doses of aminophyllin and theophylline with sodium acetate.

5. In general, patients with less severe and less frequent attacks of pain show a better therapeutic response than do those with more advanced coronary insufficiency, but a patient who responds favorably to one xanthine compound does not necessarily show a similar reaction to others; and, in some cases, no effect is demonstrable.

6. When given orally in proper dosage to certain patients with coronary sclerosis, compounds of theophylline and theobromine dilate the coronary arteries and bring about symptomatic improvement. The choice of suitable subjects and of the most effective preparation in the individual case must depend, for the present, on clinical trial.

REFERENCES

1. Levy, R. L., Bruenn, H. G., and Williams, N. E.: The Modifying Action of Certain Drugs (Aminophyllin, Nitrites, Digitalis) Upon the Effects of Induced Anoxemia in Patients with Coronary Insufficiency, AM. HEART J. **19**: 639, 1940.
2. Essex, H. E., Wegria, R. G. E., Herrick, J. F., and Mann, F. C.: The Effect of Certain Drugs on the Coronary Blood Flow of the Trained Dog, AM. HEART J. **19**: 554, 1940.
3. Green, H. D.: Effect of Pitressin, The Nitrites, Epinephrine and the Xanthines on Coronary Flow in Mammalian Hearts, Blood, Heart and Circulation, Publication of the American Association for the Advancement of Science No. 13, Science Press, 1940, p. 105.
4. Stewart, H. J., and Jack, N. B.: The Effect of Aminophyllin on Peripheral Blood Flow, AM. HEART J. **20**: 205, 1940.
5. Levy, R. L., Bruenn, H. G., and Russell, N. G., Jr.: The Use of Electrocardiographic Changes Caused by Induced Anoxemia as a Test for Coronary Insufficiency, Am. J. M. Sc. **197**: 241, 1939.
6. Levy, R. L., Williams, N. E., Bruenn, H. G., and Carr, H. A.: The "Anoxemia Test" in the Diagnosis of Coronary Insufficiency, AM. HEART J. **21**: 634, 1941.

# Department of Clinical Reports

## CONSTRICTIVE PLEURITIS AND PERICARDITIS

C. Sidney Burwell, M.D., and G. Darrell Ayer, M.D.
Boston, Mass.

THE purpose of this paper is to place on record the case of a patient who exhibited an instructive and (so far as can be found) hitherto unreported complication of tuberculous pericarditis with constriction.

### REPORT OF CASE

The patient, a 54-year-old laborer of Lithuanian birth, began in January, 1938, to suffer from coryza and cough. A few weeks later he became conscious of shortness of breath on exertion, and soon after this had dyspnea at rest, orthopnea, and swelling of the ankles. On March 12, about two months after the onset of his symptoms, he entered the Peter Bent Brigham Hospital.

At this time he had mild dyspnea when at rest. The heart rate was rapid, the rhythm regular, the pulse small. The heart was not enlarged and no murmurs were heard. The arterial blood pressure was 100/70 mm. Hg, and the venous blood pressure was 210 mm. of water. The cervical veins were visibly distended; the edge of the liver was felt 5 cm. below the costal margin; and there were signs of fluid in both pleural cavities and slight edema of the ankles. A friction rub was audible in the left axilla. At the fluoroscopic examination the excursion of the left border of the heart was considered to be less than normal, and there was no visible movement of the right border. An electrocardiogram showed low voltage, inversion of $T_2$ and $T_3$, and a normal Lead IV.

Marked improvement in comfort followed a few days of hospital care, during which time his chest was tapped and he received digitalis and mercurial diuretics. When he had lost about 16 pounds of fluid by various routes he could lie flat without dyspnea and his vital capacity was 3,100 c.c., but the peripheral venous pressure remained elevated. The basal cardiac output was measured by the acetylene method and found to be 2.2 liters per minute. The output per beat was 29 c.c. The total plasma protein was 6.5 to 7.2 (albumin 2.9 to 3.5). The temperature rarely rose above 99° F. and was usually within limits which were considered normal. The pleural fluid had a specific gravity of 1.010; there were 1,000 cells per c.mm., 98 per cent of which were small lymphocytes.

The combination of congestion of the systemic circulation, essentially clear lungs, and a small, underactive heart suggested that he had constrictive pericarditis. The greatly diminished cardiac output, the persistence of the elevation in venous pressure, and the fluoroscopic observations were regarded as compatible with this diagnosis. It appeared to be a kind of pericardial disease which is most frequently seen as the result of tuberculosis; when a guinea pig which was inoculated with the patient's pleural fluid died of tuberculosis, the etiology was considered to be established.

After a period of observation in the ward, pericardiectomy was advised, but the patient decided against operation at that time and left the hospital April 23, 1938.

From the Departments of Medicine and Pathology, Harvard Medical School and the Peter Bent Brigham Hospital, Boston, Mass.

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At home, for the ensuing ten weeks, he was up and about. The situation changed but little during this time; the degree of disability remained about the same, the venous pressure remained high, and edema accumulated unless mercurial diuretics were administered. On one occasion during this period a pleural friction rub was heard on the *right* side.

Because of the lack of improvement, operation was again suggested, and, on July 11, 1938, the patient entered the surgical service of the Peter Bent Brigham Hospital. The operation was performed by Dr. Elliot C. Cutler on July 13, 1938. He recorded the following description of the operation.

"There was a minimum of evidence of inflammatory disease in the areolar tissue between the sternum and the pericardium. The pericardium itself was tough and thick, fully 3 mm. in thickness. It was opened, and a cleavage plane found between the pericardium and the epicardium. Gradually the heart was separated from adherent pericardium, using Joker scissors, the knife, and periosteal elevator. Then the whole anterior portion of pericardium was removed. When this had been done the muscle pulsated much more vigorously, but even then a dense epicardial scar seemed to hold back the muscle considerably. I tackled this with sharp dissection with a new knife, for by no other means could I lift this scar away from the muscle, and, even so as I dissected I was sometimes shaving off bits of muscle. It was a tedious job; and I did not feel I had removed all of the epicardial scar, but at least a considerable amount came away."

The tissue which was removed showed, microscopically, dense hyaline cicatricial tissue in which occasional proliferative tubercles were embedded.

When the venous pressure was measured a few hours after operation it was found to have been reduced to normal. It fluctuated a little for the following week, but after that was never above 105 mm. of water, and was usually less than 90 mm. of water. The venous distension was visibly reduced, as was the volume of the liver. These observations indicated that the obstruction to filling of the heart had been removed by the operation.

Nevertheless, during the first week after operation he accumulated fluid in his pleural cavities and required tapping on four occasions. The fluid was greenish or amber, clear, and had a specific gravity of 1.014 to 1.018. Two weeks after operation he returned to the medical service for observation.

At this time his only discomfort was pain in the region of the wound on inspiration. There was a little fluid in each pleural cavity, but no other suggestion of congestion. His temperature (which during the week after operation had reached 103°) went as high as 100° only once. He was discharged after a week. He felt a little weak and still had slight precordial pain.

At home he found, to his disappointment, that he did not gain strength or weight. Attempts to increase his bodily activity caused severe pain in the region of his operative wound and a consciousness that he could not take a deep breath. Eight weeks after operation he was again admitted to the medical ward.

Examination at this time showed no evidence of venous distension, enlargement of the liver, or edema. The venous pressure was 96 mm. of water, the arterial pressure, 120/95 mm. Hg, and the circulation time, seventeen seconds. Fluoroscopic examination of the heart showed large hilar shadows, a small heart beat and indistinct borders, and a visible, but small, excursion of the right border. These observations were accepted as indicating that the mechanical obstruction of the constricting pericardium had been relieved by pericardiectomy.

He suffered, however, from a new and distressing disability—a grave interference with respiratory movements and a sense of inability to get his breath. He did not have orthopnea. Inspiration was sharply limited, and the vital capacity was only 600 c.c., although there was no evidence of pulmonary congestion or edema. The trachea was firmly fixed so that it did not move with respiration or deglutition.

There was a sense of difficulty in swallowing. Vigorous attempts at inspiration failed to lift the sternum and led to an apparent sucking in of the apices. Under the fluoroscope the diaphragm appeared to be not paralyzed, but fixed. The sternum did not lift, but there was some expansion of the lower chest outward, and the ribs moved upward a little. The anteroventral part of the costal margin moved inward; the axillary part, outward. Certain peculiar additional waves in the electrocardiogram were found to be linked with the recurrent muscular effort of inspiration.

These abnormalities were taken to point to a mechanical limitation of chest mobility, probably caused by involvement of the mediastinum and diaphragm in scar tissue, and not by heart failure or constriction. The ecchymosis which still surrounded the operative wound, now over two months old, was attributed to rupture of small vessels in the scar tissue by his frantic efforts to expand his chest.

He had also at this time several attacks of tachycardia with palpitation. On one such occasion electrocardiograms revealed nodal tachycardia, with a ventricular rate in the neighborhood of 200. There was some discussion of the possibility of releasing the chest surgically from whatever was preventing its expansion. This was decided against. The respiratory distress continued, and the patient died suddenly (he was found dead in bed a few minutes after he had been observed in no more than his usual discomfort) on Sept. 25. This was nine months after the onset of his symptoms and two and one-half months after the operation on his pericardium.

The description of the significant portions of the post-mortem examination is as follows:

*Thorax.*—As the anterior aspect of the thorax was opened, the heart was found to be firmly bound to the sternum by dense cicatricial tissue. A similar scar bound the anterior surface of both lungs to the chest wall. With the single exception of the cicatrix at the site of the operation on the pericardium, these collections of cicatricial tissue were confined to their respective serous cavities, and did not merge with one another or extend outside the parietal layers.

In the superior mediastinum the fat overlying the great vessels was free from active inflammation or induration. A large fibrotic lymph node bound the anterior surface of the trachea (at its bifurcation) firmly to the pericardium covering the posterior surface of the right atrium.

*Pericardium.*—Between the heart and the sternum there was a mass of cicatricial tissue occupying the area of decortication. In this mass, in an area beneath the fourth rib on the left, there was a small pocket containing 3 c.c. of yellow, puriform material. Tubercle bacilli were obtained from this material by smear and by culture. With that exception there was no gross evidence of active inflammation in the pericardium. The two pericardial layers were bound together by cicatricial tissue that filled the space but measured no more than 2 mm. in thickness (Fig. 1). This scar tissue and the heart beneath it were easily compressible. Unfortunately, no attempt was made to judge its capacity to stretch.

*Pleura.*—On both sides, tuberculous granulation tissue, with the gross appearance of a cicatrix, covered the visceral and parietal pleural surfaces in a continuous, thin layer. For the most part the two layers were fused, but inferiorly, on each side, a small cavity, containing about 30 c.c. of yellow, gelatinous fluid, remained between the layers (Fig. 2).

*Lungs.*—Through the thin pleural cicatrix the lungs were easily compressible and crepitant throughout. When the apices were sectioned no scars or active tuberculous lesions were seen. Several fibrosed, black, lymph nodes appeared along the larger bronchioles, but there was no caseation or calcification. Posteriorly, in each lower lobe, there was slight atelectasis, but elsewhere the lungs were well aerated, and pink frothy fluid was obtained on pressure. The vessels were free from thrombi.

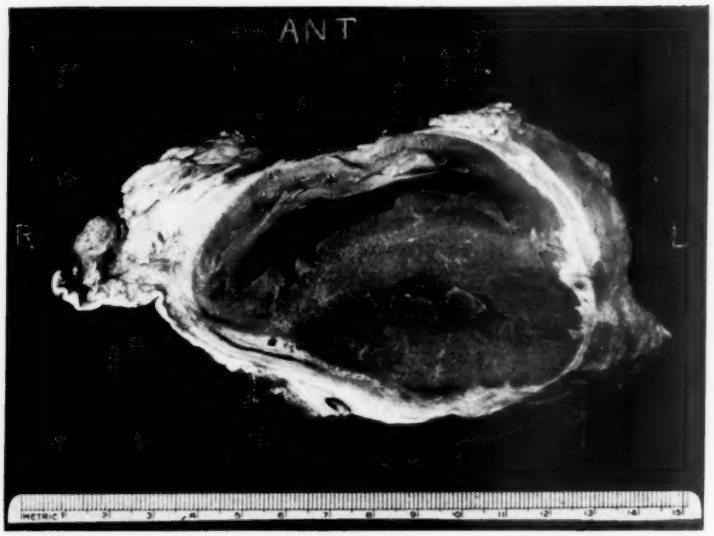


Fig. 1.—Heart and pericardium in cross section. Anteriorly, all of the cicatrix that lay between heart and sternum has been cut away. The surface on the left of the specimen is the rough pleural cicatrix which was cut across to free the heart. This gives an outer, dark layer. Next is a pale layer of extrapericardial fat, and then a dark stratum which is the tuberculous granulation tissue between the visceral and parietal pericardium. The next white stratum is the normal epicardial fat with the coronary vessels, and beneath this lies myocardium.

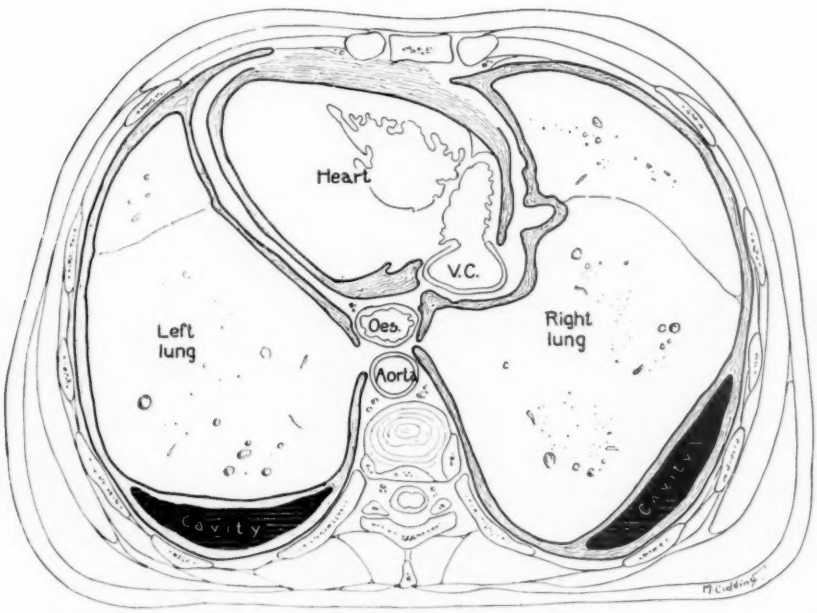


Fig. 2.—Diagrammatic cross section of the lower thorax to show the complete envelopment of the lungs by a continuous sheet of scar tissue. The tuberculous cicatrices are indicated by broken wavy lines which are drawn somewhat wider than they actually were. Posteriorly, the pleural cicatrices are separated by collections of fluid, labeled cavity. Elsewhere the two layers are fused. They are confined to their respective serous cavities except in the operative site anterior to the heart, where the postoperative cicatrix extends from the heart to the sternum.

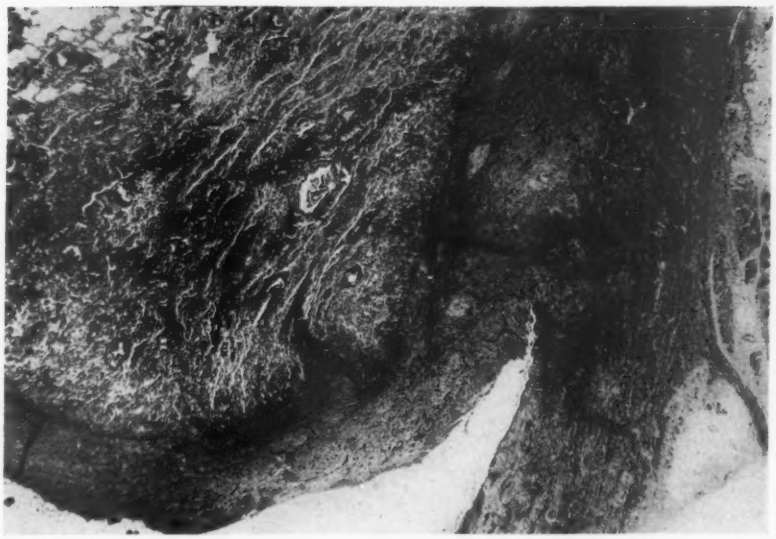

Fig. 3.—Left lung and pleura (hematoxylin and eosin stain, ×15). On the right are normal intercostal fat and nerves. To the left of this is the pleural cicatrix, and then the atelectatic peripheral portion of the lung. Below is the upper extension of the persisting pleural cavity at the left base. The thick tuberculous granulation tissue covers the pleural surfaces and fuses above to obliterate the cavity. The clear areas are active tubercles. There is no tuberculosis in the lung.

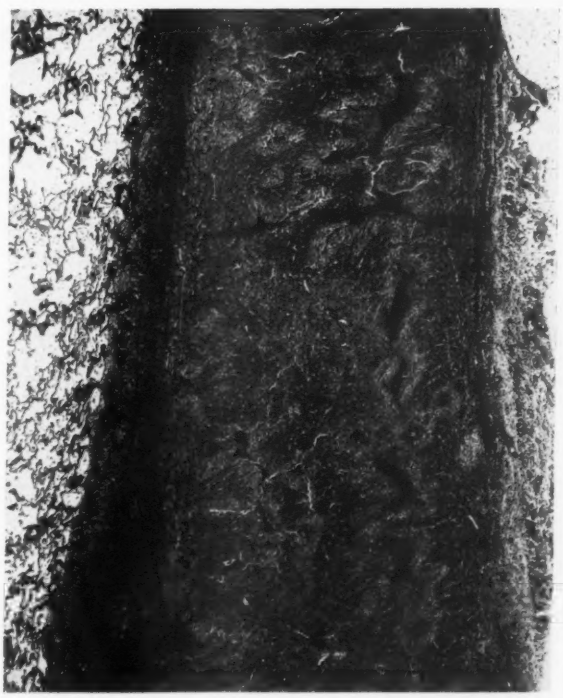

Fig. 4.—Lung and pleura near apex (hematoxylin and eosin stain, ×15). The obliteration of the pleural space has left many small irregular cavities filled with dark amorphous debris. About these is a pale collar of active tuberculous granulation tissue which shades into the denser cicatrix. The lung tissue and the intercostal fat are free from inflammation or cicatrization.

*Heart.*—Cross sections through the heart showed that the wall of the left ventricle measured 1.6 cm. in thickness, and that of the right, 1.1 cm. The valves were all normal. The superior and inferior venae cavae entered the right atrium without suffering a reduction of their caliber by the surrounding cicatrix.

The other viscera were normal in size and gross appearance. The brain was slightly edematous, but there was no evidence of inflammation or hemorrhage.

*Microscopic Examination.*—The lungs showed moderate edema, as evidenced by acidophilic granular material in the alveolar spaces. There were a few scattered microscopic areas of early bronchopneumonia. In the areas of atelectasis the alveolar walls were slightly thickened with connective tissue, and the alveolar spaces contained macrophages filled with carbon pigment and fat droplets. About four small cicatrices were found near bronchioles. These were thought to be healed tuberculous lymph nodules, but no active lesions were found. Active tuberculosis was evident only on the pleural surfaces. This tuberculous granulation tissue over the pleura was for the most part dense and rich in collagen (Figs. 3 and 4).

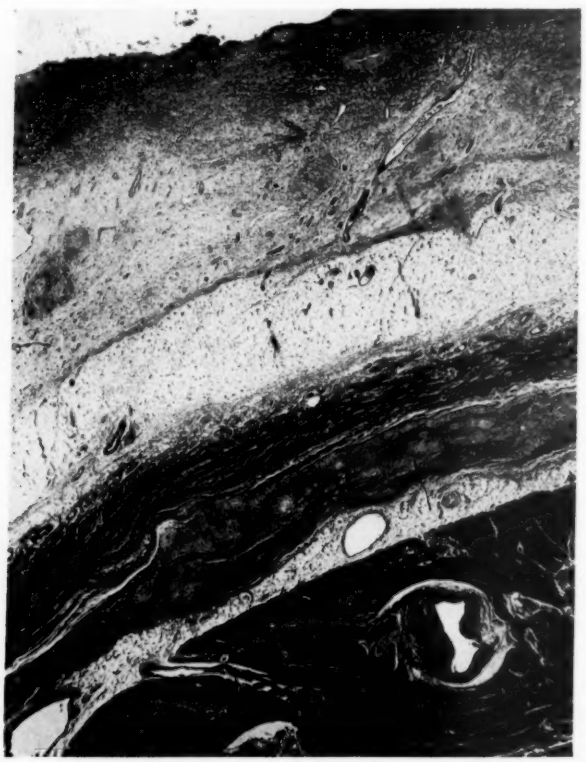

Fig. 5.—Heart and pericardium (hematoxylin and eosin stain, ×15). Above is a broad zone of tuberculous granulation tissue in the pleura, in which there are pale round active tubercles. Next is a zone of normal extrapericardial fat. Then there is a dark zone made up of normal connective tissue of the epicardium. Between this and the normal epicardial fat there is a thin stratum of dense tuberculous granulation tissue, in which the pale round areas represent tubercles.

A similar, dense, collagenous, tuberculous granulation tissue filled the pericardial space (Fig. 5). Scattered through it were many active, proliferative tubercles. The epicardial fat was free from inflammation, and the coronary vessels were normal. The heart muscle was well preserved.

The hilar lymph nodes and the lymph node between the pericardium and trachea showed no evidence of active tuberculosis. These were all replaced almost entirely by dense cicatricial tissue (Fig. 6).

Sections of spleen and liver showed a few active, recently developed tubercles, but no other organs showed evidence of tuberculosis.

A section of skin from the region of the operation was free from evidence of inflammation. In the corium there was a moderate amount of recently extravasated blood.

The tuberculous process, even in the active tubercles, was predominantly proliferative in character. This proliferation of connective tissue and the elaboration of collagen resulted in a process in which cicatrization far overshadowed the sequences of inflammation. Using "cicatrix" in this sense, the autopsy observations can be summarized as follows: A thin, tough, continuous cicatrix covered the parietal and the visceral pleura, and the two were for the most part fused. A similar cicatrix bound parietal and visceral pericardium together, except anteriorly, where a true cicatrix bound the heart to the sternum. Finally, a tuberculous lymph node in which there was the same cicatrizing type of reaction bound the trachea to the pericardium.

Fig. 6.—This shows normal trachea with lymph node adherent. The lymph node is made up almost completely of dense cicatricial tissue. The dark islands are composed of lymphocytes and carbon particles. (Hematoxylin and eosin stain, ×15.)

## DISCUSSION

In approaching the problem of explaining the disability caused by these lesions two properties of cicatricial tissues may be recalled: resistance to stretching, and a strong tendency to contraction. The work

in recent years of Churchill,[1] Volhard and Schmieden,[2] White,[3] Beck,[4] Burwell and Blalock[5] and others has served to show how such a pericardial scar may interfere with diastole. Though under these circumstances systole of the ventricle may be relatively unopposed, such interference with filling leads to a reduced stroke volume and an elevated venous pressure, with all their discomforts and dangers.

A similar limitation appears in this patient to have bound the lungs also. The normal mobility of the pleura permits expansion of the lungs during inspiration. The cicatrices which covered the whole area of visceral and parietal pleura opposed such expansion, reduced the volume of the lung at rest, and allowed only a minute and inadequate tidal volume from movement of the chest. The vital capacity fell from 3,100 to 600 c.c.

Finally, the trachea was fixed to the pericardium and the pericardium to the diaphragm. This limited further the descent of the diaphragm, and also interfered with the normal movement of the trachea during swallowing. Whether death was immediately due to cerebral edema or to some terminal cardiac disorder, such as ventricular fibrillation, it was, in either case, the result of asphyxia from mechanical interference with respiration.

This patient's course may also bring some evidence to bear on the troublesome question of whether pericardiectomy in a patient with active tuberculous pericarditis tends to "stir up" or to disseminate the infection. In this patient, it will be recalled that pleural friction rubs were heard on both sides of the chest, and that organisms were found in fluid from the left pleural cavity long before the operation. The real seat of trauma from the operation was the pericardium, yet there appeared to be no evidence of activation of the pericardial process. It appears, therefore, that the operation only relieved the mechanical obstruction to the entry of blood into the heart, and neither accelerated nor retarded the progress of the tuberculous infection.

## SUMMARY

This patient had tuberculous pericarditis with cardiac constriction, plus bilateral tuberculous pleurisy. Pericardiectomy served to relieve the cardiac tamponade. He then developed an extreme limitation of his respiratory excursion, which apparently led to his death. Autopsy revealed an actively tuberculous constrictive thickening of the pericardium covering the heart, and a similar limiting structure completely encompassing the lungs.

There was an interesting parallelism between the effect of the pericardial lesion on the heart and that of the pleural lesion on the lung. Each interfered with the expansion and filling of an organ which must expand and fill to carry out its essential function. Because of this func-

tional similarity, it appears reasonable to apply to the pleural affection the term that is accepted as descriptive of the pericardial one. Hence, it is referred to as *constrictive pleuritis.*

REFERENCES

1. Churchill, E. D.: Decortication of the Heart (Delorme) for Adhesive Pericarditis, Arch. Surg. **19**: 1457, 1929.
2. Volhard and Schmieden: Ueber Erkennung und Behandlung der Umklammerung des Herzens durch schwielige Perikarditis, Klin. Wchnschr. **2**: 5, 1923.
3. White, P. D.: Chronic Constrictive Pericarditis (Pick's Disease) Treated by Pericardial Resection, Lancet **2**: 539, 1935.
4. Beck, C. S.: Surgical Treatment of Pericardial Scar, J. A. M. A. **97**: 824, 1931.
5. Burwell, C. S., and Blalock, A.: Chronic Constrictive Pericarditis. Physiologic and Pathologic Considerations, J. A. M. A. **110**: 265, 1938.

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**Corrigendum**

In the article by F. N. Wilson and F. D. Johnston, entitled "The Occurrence in Angina Pectoris of Electrocardiographic Changes Similar in Magnitude and in Kind to Those Produced by Myocardial Infarction," which appeared in the July, 1941, issue of the Journal, Fig. 5, on page 71, was printed upside down.

# Department of Reviews and Abstracts

## Selected Abstracts

**Eckstein, R. W., Roberts, J. T., Gregg, D. E., and Wearn, J. T.: Observations on the Role of the Thebesian Veins and Luminal Vessels in the Right Ventricle.** Am. J. Physiol. 132: 648, 1941.

The role of the thebesian veins and luminal vessels of the right ventricle was studied by injecting India ink or Berlin blue into the isolated right ventricle of the beating heart.

There was no gross or microscopic injection of the myocardium when right ventricular systolic pressure was below left ventricular systolic pressure.

Gross and microscopic myocardial injection occurred only when right ventricular systolic and diastolic pressures exceeded left ventricular systolic and diastolic pressures, respectively.

Therefore, in the normally beating heart myocardial nourishment does not occur through these channels from the right ventricle.

AUTHORS.

**Neumann, C., Cohn, A. E., and Burch, G. E.: A Quantitative Method for the Measurement of the Rate of Water Loss From Small Areas, With Results for Finger Tip, Toe Tip and Postero-Superior Portion of the Pinna of Normal Resting Adults.** Am. J. Physiol. 132: 748, 1941.

A method is described for measuring the rate of water loss from small surfaces. The method consists in passing dry oxygen through chambers covering the surfaces and then conducting the moisture-containing oxygen through cold aluminum coils. From the difference in weight of the coils before and after the passage of the oxygen, the amount of water lost is learned. The method is accurate to 2.6 per cent. This error can, however, reach 9 per cent when less than 6 mg. of water are measured, but such low values were not encountered.

The rate of the elimination of water was studied from the right index finger tip, right second toe tip and posterosuperior portion of the right pinna of fifteen white, normal, resting adult subjects. The mean rate of water loss was found to be 1.86 mg. per square centimeter per 15 minutes for the finger tips, 1.18 mg. for the toe tips, and 0.48 mg. for the pinnae. The rate of water loss in the toe tips was approximately two-thirds as rapid as in the finger tips, and the rate for the pinnae was only one-quarter as rapid as that for the finger tips.

AUTHORS.

**Wiggers, C. J.: The Ineffectiveness of Vagal Stimulation on Ventricular Fibrillation in Dogs.** Am. J. Physiol. 133: 634, 1941.

In numerous trials on seventy-eight dogs in which ventricular fibrillation was induced by various means and at various times during the course of an experiment, stimulation of the vagus nerves by strong faradic shocks and at different times after onset of fibrillation never restored normal coordinated beats nor produced convincing changes in the usual trend of the fibrillating process. Two corollaries fol-

low: 1, the method is obviously without value as a resuscitating agent; and 2, crucial proof that the vagus has any effect on the fibrillating or normally contracting dog's ventricle still remains to be produced.

AUTHOR.

**Wégria, R., Moe, G. K., and Wiggers, C. J.: Comparison of the Vulnerable Periods and Fibrillation Thresholds of Normal and Idioventricular Beats.** Am. J. Physiol. **133**: 651, 1941.

Our results indicate 1, that even in fresh hearts the vulnerable period of premature beats is extended nearly to the end of the isometric relaxation process, but 2, that the fibrillation threshold is not significantly altered. The first demonstration supplies supplementary evidence in harmony with our conception of the induction of fibrillation following coronary occlusion (4). On the other hand, we cannot confirm our interpretation that weak, prolonged, direct currents induce fibrillation when opening of the current occurs during the vulnerable period of a premature systole which has a reduced threshold.

Our results are also interesting in crystallizing our conception as to the ultimate processes which underlie the initiation of fibrillation. An asynchronous offset of fractionate contractions, caused either by a slight delay in their onset or by variations in their durations, is, as King has emphasized, considered essential to any concept as to how fibrillation starts. Our results certainly fail to show that a greater degree of asynchronicity in termination of contractions in premature beats reduces the fibrillation threshold. The sensitivity to fibrillation, therefore, seems to depend rather on some inherent characteristic of cardiac muscle at the beginning of the relaxation of its ultimate units. This is supported by our observations that the period of vulnerability is extended in beats which arise from an ipsiventricular focus. That is not solely due to greater difference in the termination of fractionate contractions—as we had postulated—is indicated by the facts 1, that the degree of extension is too great, and 2, that a similar extension occurs in normally excited ventricles with impaired function.

AUTHORS.

**Leary, T.: Symposium on Sudden Death. Syphilitic Aortitis as a Cause of Sudden Death.** New England J. Med. **223**: 789, 1940.

Syphilitic aortitis is associated with overstimulation of the essential aortic blood vascular system, the vasa vasorum. With the excessive growth of blood vessels, which penetrate through the media into the intima, there is an excessive growth of fibroblastic tissue, which thickens the intima and tends to narrow and occlude the portions of the coronary arteries lying within the aortic wall. Marked narrowing or occlusion of the ostia may result in sudden death, of coronary type, in the early stages of the disease.

In addition to widening of the commissures and rolling of the cusps, the association of atherosclerosis with late syphilitic aortitis tends to be followed by calcification and diffuse dilatation of the aorta, including the ring. Dilatation of the ring produces aortic insufficiency, which may be followed by sudden death, of coronary type, but usually leads to late progressive cardiac decompensation. Rupture of aneurysms is also a cause of sudden death, as is the production of local dissecting aneurysms in the lower ascending aorta, with rupture into the pericardium.

Experimental atherosclerosis in the rabbit following the feeding of cholesterol results in late diffuse dilatation of the aorta resembling that found in combined syphilitic aortitis and atherosclerosis in man.

AUTHOR.

**Weiss, S.: Symposium on Sudden Death. Instantaneous "Physiologic" Death.** New England J. Med. 223: 793, 1940.

In cases of sudden death, post-mortem examination frequently fails to explain the mechanism of death. In the majority of cases the underlying structural lesions are chronic, and lesions of the same type may be found in cases in which they do not contribute to the cause of death. In cases of instantaneous death fresh lesions responsible for death are often absent. In the causation of instantaneous death, a hyperirritable myocardium of anoxic or infectious origin and hyperactive reflexes singly or in combination play the most important roles. The functional capacity of the heart before death in these cases may be adequate or good. The determining factor in instantaneous death is often physiologic.

The general nature of syncopes is discussed. Evidence favors the concept that instantaneous death is often a fatal syncope. Asystole of various types and ventricular fibrillation are the usual causes.

AUTHOR.

**Moritz, A. R.: Symposium on Sudden Death.** New England J. Med. 223: 798, 1940.

Although this discussion of the causes of sudden death is in no sense complete, it includes some of the more important diseases that commonly predispose to unexpected collapse and death. They do so for one of two principal reasons. The disease may render the circulatory system hyperirritable, so that a minor stimulus or stress causes the latter to fail, or the disease may be suddenly converted from a condition that is compatible with life into one that is incompatible.

From a medical standpoint the chief interest in sudden death lies in the fact that its occurrence is often unnecessarily premature. Death may be the result of an avoidable trespass on the physical or functional reserve of the diseased part. This is particularly true in cases of sudden death from heart failure. If the diseased condition were recognized so that the person so affected could be advised how to live within the limits of his diminished reserve, there would be less likelihood of the commission of fatal physical or emotional excesses.

For the protection of such a patient and of persons who might be injured by him, he should be advised against any undertaking in which his sudden collapse might lead to physical injury to himself or others. It is apparent that a person threatened with sudden loss of consciousness should not drive an automobile, operate a public conveyance, or otherwise engage in potentially dangerous undertakings.

From a medicolegal standpoint the subject of sudden death is of great importance. On the ability of the medical examiner to recognize the lesions responsible for sudden death from natural causes may depend whether an obscure death leads to a criminal indictment or to no charge, or whether or not it results in a civil action for indemnification. Thus, the difference between a verdict of murder and an acquittal may rest on post-mortem evidence. The difference between double and single indemnity in the settlement of insurance claims or the difference between full workmen's compensation and no compensation is likewise apt to be dependent on evidence obtained at autopsy.

The investigation of the causes of sudden death constitutes a problem of far-reaching medical and medicolegal significance.

AUTHOR.

**Kaplan, L. G., and Katz, L. N.: The Characteristic Electrocardiograms in Left Ventricular Strain With and Without Axis Deviation.** Am. J. M. Sc. 201: 676, 1941.

The electrocardiographic patterns seen in 178 instances (twenty-four necropsied) of left ventricular strain are described.

The characteristic development of the classical S-T-T complex in left ventricular strain is emphasized.

The classical types and intermediate forms are described and the natural evolution of these is presented.

Approximately 15 per cent of the total cases in the present series did not show any axis deviation and 62.5 per cent of these had the classical S-T-T deviation in Lead I. This latter type is called the concordant type of left ventricular strain. It formed 19 per cent of all the cases with characteristic S-T-T changes in Lead I.

It was not possible to correlate heart size and the type of electrocardiographic pattern in left ventricular strain.

Accompanying right ventricular strain, either as a late result of left ventricular or of an associated independent cause, and changes in the heart's position are the probable chief causes for lack of axis deviation in the concordant type of left ventricular strain.

The S-T-T deviation in left ventricular strain is attributable to a distance in the retreat of activity in the ventricles, in part due to the hypertrophy itself and in part secondary to coronary insufficiency.

The practical importance of recognizing the concordant type of electrocardiogram in left ventricular strain is emphasized.

AUTHORS.

**Scherf, D., and Weissberg, J.: The Alterations of the T Waves Caused by a Change of Posture.** Am. J. M. Sc. 201: 693, 1941.

The phenomenon of flattening or inversion of a formerly positive T wave in Lead III in the upright position was studied in thirty-five patients. This inversion increased during deep inspiration and decreased at the end of maximum expiration with upward pressure on the diaphragm.

These observations speak against the assumption that cardiac damage or anoxia of the heart muscle can be the factor responsible for the electrocardiographic alterations. They confirm the conception that the inversion of the T wave is due to a change in posture, and therefore a change in contact between the heart and the neighboring tissues.

AUTHORS.

**Flaxman, N.: Atrioventricular Nodal Rhythm.** Am. J. M. Sc. 201: 857, 1941.

Atrioventricular nodal rhythm is an infrequent cardiac conduction disturbance which can be diagnosed only with the aid of the electrocardiograph. Its importance rests chiefly on the two facts that it is due to a large variety of causes, both cardiac and extracardiac, and that it indicates depression of the normal pacemaker of the heart, the sinoauricular node.

Neither digitalis nor quinidine, nor any other special drug is indicated in treatment since nodal rhythm does not tend to persist after the cause has subsided or has been removed. Treatment, if possible, should be directed against the underlying cause.

AUTHOR.

**Blackford, L. M., and Parker, F. P.: Pulmonary Stenosis With Bundle Branch Block: Report of a Case With Sound Tracings and Semiserial Studies of the Conduction Bundle.** Arch. Int. Med. **67**: 1107, 1941.

A case is presented of pulmonary stenosis with right bundle branch block occurring in a man who died at 23. Congenital pulmonary stenosis was diagnosed several years before his death, but the electrocardiogram was interpreted as evidence of a septal defect.

Sound tracings lend little support to the opinion that bundle branch block can be diagnosed with the stethoscope.

Histologic studies confirm the thesis that the cause of bundle branch block is often interference with the blood supply of the interventricular septum.

Paroxysms of tachycardia in cases of serious heart disease indicate a grave prognosis.

AUTHORS.

**Bain, C. W. C.: Variable Ventricular Complexes in Heart Block, and Their Relation to Bilateral Bundle Branch Block.** Brit. Heart J. **3**: 75, 1941.

Four cases of A-V heart block with varying ventricular complexes have been observed. In two the A-V block was nearly always complete, although retrograde conduction occurred at times from ventricle to auricle; in the other two the A-V block varied. Analysis of the curves obtained suggests that bilateral bundle conduction defects were present in all of these cases. In three the evidence pointed to multiple centers of impulse formation, and these all died from Stokes-Adams disease; in one it was concluded that variable conduction was taking place down each branch from a single idio-ventricular center, and he has had no Stokes-Adams attacks.

Varying ventricular complexes in A-V heart block usually signify the presence of bilateral bundle conduction defects.

The impulses may arise from one or more places in the ventricles. Multiple foci of origin increase considerably the risk of Stokes-Adams attacks.

The duration of the QRS in bundle branch block is in part a measure of the speed of conduction in the relatively healthy branch; in bilateral bundle lesions the accepted minimum must always be exceeded. In those cases in which one branch is conducting normally, this minimum width may not exceed 0.11 sec.

Some forms of atypical right branch block may represent incomplete right branch block, the wide QRS being due to the presence of bilateral defects.

AUTHOR.

**Barber, H., and Osborn, G. R.: A Fatal Case of Myocardial Contusion.** Brit. Heart J. **3**: 127, 1941.

A fatal case of contusion of the myocardium has been described: there was no rupture of the heart muscle. The morbid anatomy has been compared with other records.

Reference is made to clinical histories, already published from this hospital, suggestive of recovery from contusion of the myocardium.

AUTHORS.

**Wechsler, H. F., Farmer, L., and Urban, J. A.: A Case of Insulin Allergy Simulating Coronary Occlusion.** J. Lab. and Clin. Med. **26**: 1090, 1941.

The sodium ion depresses the blood sugar level in rabbits. In juvenile diabetic patients the administration of sodium salts decreases both blood sugar level and glycosuria. The mechanism of this action is unknown.

Potassium salts increased the blood sugar concentration and glycosuria of juvenile diabetic persons. This effect appears to be due to a stimulating effect on adrenalin discharge and is inhibited by magnesium.

There is no unanimity of opinion concerning the effect of calcium on the glycemic levels of various experimental animals. Calcium salts appear to depress the hyperglycemic effect of epinephrine in animals.

Nickel and cobalt salts, when added to insulin, delay the effect of the latter in normal rabbits and dogs, but not in diabetic human beings. Nickel and cobalt salts, when given alone, have no effect on blood sugar level of man or animals.

Zinc-deficient diet delays the absorption of carbohydrate from the gastrointestinal tract of rats. Zinc oxide has been found to produce glycosuria in dogs and pancreatic fibrosis in cats. The zinc content of the pancreases of diabetic persons is greatly below normal.

Zinc, aluminum, ferric chloride, nickel, or cobalt, when mixed with insulin, delays the action of the latter; calcium, magnesium, and potassium alum do not delay the effect of insulin when mixed with it.

Lead and manganese decrease the fasting blood sugar levels.

Phospho-24-tungstic acid, phosphomolybdic acid, molybdic acid, silico-tungstic acid, sodium tungstate, and ammonium phospho-18-tungstate appear to cause a decrease in blood sugar of diabetic persons.

Glycosuria has been observed after the administration of mercury, uranium, and chromium.

The administration of copper salts, both in man and animals, causes a decrease in the ability of adrenalin to mobilize liver glycogen.

AUTHORS.

**White, P. D., and Bland, E. F.: Mitral Stenosis After Eighty.** J. A. M. A. **116**: 2001, 1941.

Four patients with mitral stenosis of moderate degree, proved at autopsy, survived the age of 80 years, two men aged 83 and 81, and two women aged 82 and 83. The first patient of the group, unaware of his heart trouble, carried on an active and eminently useful medical career, was a leader of his generation, and himself wrote on the good prognosis of many cases of rheumatic heart disease.

AUTHORS.

**Cossio, P., Berconsky, I., and Gamba, R.: Pulmonary Stenosis and Nodular Ossification of the Lungs.** Rev. argen. de cardio. **7**: 385, 1941.

A case is described of cor pulmonale of subchronic evolution with multiple nodular ossification of the lungs verified at autopsy.

The nodular ossification of the lungs was due to a process of metaplasia of the connective tissue caused by a bronchioalveolar and arteriolar chronic inflammatory state. It is believed that the excess of work of the right ventricle was a consequence of the diminished diameter of the pulmonary arterioles.

The electrocardiographic alterations observed (deep S I and S II, negative T III and T IV) are believed to be due to disturbances in the metabolism of the heart muscle as a result of fatigue of the strained right ventricle, and not to a pulmocoronary reflex.

Cor pulmonale and multiple nodular ossification of the lungs should be considered in the diagnosis whenever multiple nodular micronodular shadows are radiologically verified in the lungs accompanied by cardiac disturbances and the described electrocardiographic alterations.

AUTHORS.

**Hubbard, J. P.: Paroxysmal Tachycardia and Its Treatment in Young Infants.** Am. J. Dis. Child. **61**: 687, 1941.

Nine cases of paroxysmal tachycardia occurring in young infants are reviewed. The fact that six of these were observed during one year stands in contrast to the sparsity of well-established cases in the literature and indicates that such cases may occur more often in the early months of life than has heretofore been recognized.

In these nine cases and in nineteen collected from the literature, in all of which the infants were less than 1 year old, there is a distinctive clinical course which in certain respects differs from that in cases of paroxysmal tachycardia in older children or in adults. The heart rate is usually 250 to 300, and if the tachycardia continues for several days, as it is likely to do, it brings on circulatory failure, which is associated with vomiting, dyspnea, fever, leucocytosis, cardiac enlargement, pulmonary possibility and engorgement of the liver. Failure to bear in mind the possibility that paroxysmal tachycardia is present in a young infant may lead to such misdiagnoses as pneumonia or congenital idiopathic hypertrophy of the heart. Paroxysmal tachycardia in young infants may be severe and may have a fatal termination if untreated, but so far as present experience indicates, the disease responds satisfactorily to adequate doses of digitalis.

AUTHOR.

**Kuttner, A. G., and Krumwiede, E.: Observations on the Effect of Streptococcal Upper Respiratory Infections on Rheumatic Children: A Three-Year Study.** J. Clin. Investigation **20**: 273, 1941.

The effects of three outbreaks of streptococcal upper respiratory infections during three successive winters in a colony of rheumatic children are described. Each of these outbreaks was due to infections with a single type of Group A beta hemolytic streptococci, but during each epidemic a different type was prevalent.

The incidence of rheumatic recurrences following these streptococcal upper respiratory infections varied greatly—from none to a large proportion of the cases.

A comparison of the epidemic strains failed to reveal any significant differences which might account for the variations in the incidence of rheumatic recurrences.

A comparison of the rheumatic histories of children who escaped and of those who developed rheumatic recurrences following pharyngitis due to "effective" strains of streptococci likewise did not show any striking differences. Our findings suggest that the vulnerability of the rheumatic subject to the effect of streptococcal upper respiratory infections is variable, and depends on factors which at the present time are not understood.

No rheumatic recurrences were observed in children who escaped streptococcal upper respiratory infections during the three-year period.

AUTHORS.

**Reyersbach, G., Lenert, T. F., and Kuttner, A. G.: An Epidemic of Influenza B Occurring in a Group of Rheumatic Children Concurrent With an Outbreak of Streptococcal Pharyngitis; Clinical and Epidemiological Observations.** J. Clin. Investigation **20**: 289, 1941.

An outbreak of influenza due to a recently described influenza virus, Influenza B (2), in a relatively isolated group of rheumatic children has been described.

The clinical symptoms were mild and remained remarkably uniform throughout the epidemic. No complications of any kind developed.

The characteristic laboratory finding was a relative leucopenia.

No evidence was obtained to suggest that the virulence of a Group A *Beta hemolytic streptococcus* of proved pathogenicity was increased by this strain of influenza virus.

Rheumatic recurrences were not precipitated by the influenza outbreak.

AUTHORS.

**Walsh, B. J., and Sprague, H. B.: Character of Congestive Failure in Children With Active Rheumatic Fever.** Am. J. Dis. Child. **61**: 1003, 1941.

The clinical features of congestive failure in children with rheumatic heart disease are described, the observations being based on a study of forty-four children between the ages of 3 and 15 years who were seen between July 1, 1937, and April 1, 1940, at the House of the Good Samaritan.

The initial signs of heart failure in these forty-four children with rheumatic fever and congestive failure were enlargement of the liver and puffiness of the face accompanied by unexpected gain in weight. A few children with congestive failure and active rheumatic fever preferred to lie flat in bed. These children had marked puffiness of the face, which caused them to look as if they had primary renal disease.

Pulmonary râles were seldom heard in these children, their appearance being limited to the terminal stages of the illness.

Other important evidences of congestive failure in children with rheumatic fever and congestive failure were high venous pressure apparent at the onset of the failure, a shift of the electrical axis of the heart to the right, which increased with progression of the heart failure and decreased or disappeared with the patient's improvement or recovery, and a well-marked diastolic gallop rhythm along the upper left sternal border.

AUTHORS.

**Corbit, J. D., Jr.: The Effect of Pregnancy Upon Experimental Hypertension in the Rabbit.** Am. J. M. Sc. **201**: 876, 1941.

A study was made of the fluctuations in: a, blood pressure; b, blood urea; and c, in the excretion of urinary protein during pregnancy in normal rabbits, and in rabbits in which arterial tension was previously raised by the experimental induction of renal ischemia.

It was found in both groups of animals that pregnancy tended to bring about a lowering of the systolic pressure a few days before the onset of labor. The extent of this fall amounted to about 20 per cent of the pre-pregnancy tension. The return of pressure to the pre-pregnancy level occurred gradually during the first two to three weeks post partum.

In the normal animal these fluctuations of arterial tension were not accompanied by significant alterations of blood urea, nor by proteinuria. In the renal ischemic animals, however, there was a coincidental, slight, prepartal fall of blood urea, and a tendency to proteinuria. In no animal was there evidence to indicate that these changes were due to ill health. The normal gestational increase of maternal body weight took place, the pregnancies were normal in duration, and the number of pups born was normal for this species.

The extent of the prepartal fall of blood pressure was proportionate to the number of fetuses present.

AUTHOR.

**Garreton-Silva, A., Croxatto, R., Fuenzalida, O., and Viveros, R.: Experimental Investigation of Pressor Substance With Blood of Patients With Arterial Hypertension.** Rev. argent de cardiol. **8:** 1, 1941.

Citrated plasma from human arterial or venous blood was perfused through a Läwen-Trendelenburg preparation using the Chilean frog.

The plasma from twenty-eight adult patients with different types of hypertension, when mixed with Page's renin activator (hypertensin precursor) produced in all cases a vasoconstrictor action. Hypertensive plasma or activator was inactive when perfused alone and normal plasma alone or mixed with the activator, showed also no vasoconstrictor action.

The presence of vasoconstrictor substances related to renin (angiotonin or hypertensin) in the blood of hypertensive subjects seems to indicate that Goldblatt's phenomenon (renal ischemia) plays a role in the pathogenesis of those cases.

AUTHORS.

**Riggs, Theodore F., and Satterthwaite, Richard W.: Unilateral Kidney With Partial Occlusion of the Renal Artery Associated With Hypertension: Case Report.** J. Urology **45:** 513, 1941.

An unusual anomaly of a single kidney and ureter on the right side, with obstruction of the renal artery by a small dissecting aneurysm and a localized sclerotic plaque, is reported.

The development of hypertension in its acute phase in this case may have been initiated by the partial occlusion of the lumen of the main renal artery and its three branches by this aneurysm.

Cases of hypertension, especially those of sudden onset, no matter what the age of the patient, would appear to warrant complete investigation of the renal arteries for abnormalities.

AUTHORS.

**Johnson, Carl A.: A Study of the Clinical Manifestations and the Results of Treatment of Twenty-Two Patients With Raynaud's Symptoms.** Surg. Gynec. & Obst. **72:** 889, 1941.

The results of a study of twenty-two patients with Raynaud's syndrome are presented with the following opinions:

1. Observations on this series of patients confirm Hutchinson's statement made more than fifty years ago that what is known as Raynaud's disease is not a clinical entity, and that the peripheral manifestations observed are merely symptoms of some more fundamental disease.

2. The vascular changes during a Raynaud's attack are not necessarily due to an active vascular constriction, but may be the results of a vasodilatation in the palmar arch with a diversion of blood from the fingers and a passive collapse of the vessels.

3. In this series of patients, surgery of the sympathetic nervous system was a therapeutic failure but medical management gave considerable relief in a number of patients.

AUTHOR.

**Hussey, H. H., and Katz, S.: The Comparative Value of Ether and Paraldehyde as Agents for Measurement of the Arm to Lung Circulation Time in Fifty Patients With, and Fifty Patients Without Heart Failure.** Am. J. M. Sc. **201:** 669, 1941.

Measurement of the circulation time is useful in the diagnosis and study of a number of diseases, and especially of heart failure.

A comparison of the relative value of ether and paraldehyde for measurement of the arm-to-lung circulation time is presented. These two drugs have already been reported to give approximately equal results in normal persons. This has been confirmed in our studies in fifty patients having no cause for delay of the circulation time.

Comparison of circulation time measurements obtained almost simultaneously by means of ether and paraldehyde in each of fifty patients with heart failure shows that measurements with paraldehyde are usually significantly longer than those with ether. Such differences constitute an inaccuracy which may be misleading clinically.

Speculation as to the possible reasons for the discrepancy in measurements made with ether and paraldehyde is offered, and the conclusion drawn that ether is the agent of choice for estimation of the arm-to-lung circulation time.

AUTHORS.

**Bedford, D. E., and Lovibond, J. L.: Hydrothorax in Heart Failure.** Brit. Heart J. 3: 93, 1941.

Old and recent views on hydrothorax have been reviewed and its clinical and radiologic diagnoses have been discussed.

Hydrothorax was observed at some stage in 136 (38.5 per cent) of 356 cases of congestive heart failure, diagnosis being mostly radiologic, and in 45 (41.3 per cent) of 109 cases of failure examined post mortem. The hydrothorax was right-sided in sixty-eight cases, left-sided in forty-two, and bilateral in twenty-six; this included eleven interlobar effusions. Neither these nor previous statistics show right unilateral hydrothorax to be as predominant as generally supposed.

A definite relation was found between the site of the hydrothorax and the underlying heart condition. Hypertension, left heart failure, and normal rhythm favored a left hydrothorax; mitral stenosis, combined right and left heart failure, and auricular fibrillation favored a right hydrothorax. Clinical hydrothorax, which clears up rapidly with treatment, can rarely be attributed to pulmonary infarction, but in the terminal stages of heart failure and at post mortem examination infarction is often an associated condition.

Hydrothorax is not uncommon in left heart failure, when it is a complication of pulmonary congestion. This explains its occurrence without edema. In pure right heart failure ascites without hydrothorax is the rule.

The pleural fluid in hydrothorax may show some degree of inflammatory reaction, probably due to its contact with chronically congested lungs, and no sharp division between transudate and exudate (cardiac pleurisy) can usually be made.

In response to treatment by mercurial diuretics, hydrothorax often clears up completely within a few weeks or months, leaving no residue; but occasionally it becomes chronic and persists for a year or longer.

The pathogenesis of hydrothorax has been discussed and reasons given for regarding it as related to pulmonary rather than systemic venous engorgement, and as a transudate from the visceral rather than the parietal pleura. Unilateral and interlobar hydrothorax can better be explained in terms of pulmonary than of systemic stasis.

AUTHORS.

**Sauer, P. K.: The Choice of Anesthesia in Operative Patients With Heart Disease.** Am. J. Surg. 48: 532, 1940.

The most common types of heart disease have been discussed from the standpoint of a choice of anesthetics.

Anesthetics have been chosen for each type of heart disease that will involve the least risk.

Contraindications to certain anesthetics in various types of heart disease have been emphasized.

A suggestion for the improvement of the service by a more careful consideration in the choice of anesthetics by both the surgeon and the anesthetist has been made.

AUTHOR.

**Wood, P.: Da Costa's Syndrome (or Effort Syndrome) (Goulstonian Lectures to the Royal College of Physicians of London, 1941).** British Med. J. 1: 767, 1941.

The symptoms and signs of Da Costa's syndrome more closely resemble those of emotion, especially fear, than those of effort in the normal subject.

The mechanism of the somatic manifestations depends upon central stimulation, not upon hypersensitivity of the peripheral autonomic gear.

This central stimulus is emotional, and is commonly the result of fear.

The reaction becomes linked to effort by a variety of devices, which include misinterpretation of emotional symptoms, certain vicious circular patterns, the growth of a conviction that the heart is to blame, consequent fear of sudden death on exertion, conditioning, and hysteria.

Incapacity tends to be exaggerated consciously or subconsciously in order to protect the individual from further painful emotional experience.

Treatment in the Army is shackled by inability to remove the distressing environmental factors which have caused or have aggravated the breakdown; by the difficulty in establishing intimate contact with a patient who did not choose his medical confidant; by the duty of having to serve the State first, the patient second.

It is urged that the diagnosis of "effort syndrome" be dropped. A proper psychiatric diagnosis is nearly always available; if attention is to be called to the presence of effort intolerance, let effort intolerance be added in brackets.

AUTHOR.

**Lichtman, S. S., and Bierman, William: The Treatment of Subacute Bacterial Endocarditis.** J. A. M. A. 116: 286, 1941.

Among 200 cases of subacute bacterial endocarditis due to *Streptococcus viridans* and nonhemolyticus collected from the literature and the records of the Mount Sinai Hospital in which the sulfonamide drugs were administered, recovery occurred in twelve, an incidence of 6 per cent recovery.

Among forty-three patients treated with combined chemotherapy and heparin, five recovered, an incidence of 11.5 per cent recovery.

Among twenty-four patients treated by chemotherapy and physically induced hyperthermia, four recovered, an incidence of 16 per cent recovery. Of twenty-one patients treated by chemotherapy and hyperthermia induced by intravenous typhoid-paratyphoid vaccine, five recovered, an incidence of 25 per cent recovery.

The number of cases in the three series treated by combined methods is still too small to yield an accurate statistical estimate of the incidence of recovery in each group. This preliminary review of the results obtained thus far is encouraging. The combined methods of therapy seem to promise a greater incidence of recovery than may be anticipated in the natural course of the disease or after treatment with the sulfonamide drugs alone.

AUTHORS.

# Book Review

CLINICAL ASPECTS OF THE ELECTROCARDIOGRAM: By Harold E. B. Pardee, M.D., Assistant Professor of Clinical Medicine, Cornell University Medical College, Ed. 4, 434 pages, 102 figures, Paul B. Hoeber, Inc., New York and London, 1941, $5.75.

The first edition of this deservedly popular book, which was published in 1924, was quickly recognized as one of the best texts on clinical electrocardiography. As each successive edition appeared, this reviewer has always included it among the books recommended to those who desired more than a bowing acquaintance with the subject. The present edition has been revised and brought up to date. It maintains the high standard of the previous editions.

Since the author has grown up, as it were, with his subject, and has been an outstanding investigator, clinician, and teacher for over twenty years, he is eminently qualified for his task. In dealing with a literature so voluminous as that of clinical electrocardiography, the selection of material for a book of this kind becomes a matter of major importance. This has been done with discriminating judgment.

Among the excellent features is the chapter entitled "The Normal Electrocardiogram," which covers forty-four pages. Careful study of this chapter and the one entitled "Hypertrophy of the Chambers of the Heart" will prove particularly helpful to those who wish to learn how to interpret electrocardiograms.

The author remains a convinced adherent of the Einthoven equilateral triangle hypothesis and accounts for all electrocardiographic deflections in limb leads on this basis. In his discussion of the theory of the electrocardiogram one obtains no inkling of the fact that there are dissenters from the faith in Einthoven's famous group of assumptions. Even Eyster's fundamentally important contribution, "The Nature of the Electrical Field Around the Heart," which has done much to impair the prestige of the triangle hypothesis, is not mentioned in this connection. This is to be regretted, for the attacks made during the past few years on the validity of the assumptions which underlie the hypothesis cannot be ignored much longer. However, no fair-minded person would criticize the author for his adherence to a view which has not only survived for nearly thirty years, but is still venerated by the majority of workers and taught in practically all textbooks.

It is a pleasure to welcome and recommend this new edition of a carefully prepared book which will doubtless continue to serve a very useful function as an introduction to clinical electrocardiography.

CHARLES C. WOLFERTH.

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THE American Heart Association stands alone as the national organization devoted to educational work relating to diseases of the heart. Its Board of Directors is composed of twenty-seven physicians representing every portion of the country.

The Section for the Study of the Peripheral Circulation was organized in 1935 for the purpose of stimulating interest in investigation of all types of diseases of the blood and lymph vessels and of problems concerning circulation of blood and lymph. Any physician or investigator in good standing may become a member of the section after election to the American Heart Association and payment of dues to that organization.

To coordinate and distribute pertinent information, a central office is maintained, and from it issues an ever widening stream of books, pamphlets, charts, posters, films, and slides. These activities all concern the recognition, prevention or treatment of the leading cause of death in the United States, diseases of the heart. The American Heart Journal is under the editorial supervision of the Association.

The income from membership and donations provides the sole support of the Association. Lack of adequate funds seriously hampers more widespread educational and research work imperative at this time. Great progress has been made, but much remains to be done.

Annual membership is $5.00 a year and journal membership at $11.00 includes a year's subscription (January-December) to the American Heart Journal and annual membership in this Association. A cordial invitation to join in this crusade is extended to you.

The American Heart Association solicits your support to the end that it may continue more effectively the campaign to which it has devoted all its energy.

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